ETHOPROP

RISK CHARACTERIZATION DOCUMENT

Medical Toxicology and Worker Health and Safety Branches
Department of Pesticide Regulation
California Environmental Protection Agency

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EXECUTIVE SUMMARY

INTRODUCTION

Ethoprop is an organophosphate pesticide, which acts in animals by inhibiting the cholinesterase enzyme. It is used in agriculture as an insecticide, nematicide and fungicide (suppression of white mold on peanuts) on food and non-food crops. The latest figures (1993) indicate an annual use in California of 62,143 pounds (28,250 kg) mostly on potatoes (97.2%). Ethoprop was the subject of a Registration Standard and a Guidance Reregistration Document issued by the U.S. Environmental Protection Agency in 1983 and 1988, respectively. Due to its high acute toxicity, formulations containing more than 40% ethoprop are classified as "restricted".

Ethoprop entered the risk assessment process due to its high acute toxicity, possible oncogenicity, and adverse effects on the liver caused by chronic exposure.

THE RISK ASSESSMENT PROCESS

The risk assessment process consists of four aspects: hazard identification, dose response assessment, exposure evaluation, and risk characterization.

Hazard identification entails review and evaluation of the toxicological properties of each pesticide. The dose-response assessment then considers the toxicological properties and estimates the amount which could potentially cause an adverse effect. The amount which will not result in an observable or measurable effect is called the No-Observed-Effect Level, NOEL. A basic premise of toxicology is that at a high enough dose, virtually all substances will cause some toxic manifestation. Chemicals are often referred to as "dangerous" or "safe", as though these concepts were absolutes. In reality, these terms describe chemicals which require low or high dosages, respectively, to cause toxic effects. Toxicological activity is determined in a battery of experimental studies which define the kinds of toxic effects which can be caused, and the exposure levels (doses) at which effects may be seen. State and federal testing requirements mandate that substances be tested at doses high enough to produce toxic effects, even if such testing involves chemical levels many times higher than those to which people might be exposed.

In addition to the intrinsic toxicological activity of the pesticide, the other parameters critical to determining risk are the exposure level, frequency and duration. The purpose of the exposure evaluation is to determine the potential exposure pathways and the amount of pesticide likely to be delivered through those routes.

The risk characterization then integrates the toxic effects observed in laboratory studies conducted with high dosages of pesticide, to potential human exposures at low dosages. The likelihood of potential, non-oncogenic adverse health effects in people is generally expressed as the margin of safety- a ratio. The dosage which produced no effects in laboratory studies is divided by the human exposure dosage to obtain the margin of safety. For oncogenic effects, the excess lifetime risk of cancer is determined by multiplying the cancer potency (slope) of the pesticide times the estimated exposure dosage.

TOXICOLOGY

Based on the currently available toxicity information, the Department of Pesticide Regulation (DPR) has concluded that acute exposure to ethoprop causes inhibition of acetylcholinesterase in the central nervous system of rats and rabbits, resulting in emaciation, soft stools, and urine and fecal staining of the fur. Ethoprop caused no histopathological or clinical signs of delayed neurotoxicity. Ethoprop was not teratogenic in rats or rabbits, and did not cause reproductive toxicity. Chronic oral exposure of dogs to ethoprop resulted in liver toxicity. Ethoprop caused chromosomal aberrations *in vitro*, and produced positive results in a dominant-lethal test, but it did not cause unscheduled DNA synthesis, nor was mutagenic activity indicated in microbial systems, with or without metabolic activation. Ethoprop exhibited oncogenic potential in rats but not mice.

EXPOSURE ANALYSIS

Estimates of occupational exposures were based on monitoring data, and calculations from monitoring data for surrogate active ingredients with similar chemical properties and application rates. Mixer/loader/applicators and incorporators working with the emulsifiable concentrate containing 70% ethoprop had greater work-related exposures than those individuals working with other formulations containing less ethoprop.

Analyses of theoretical dietary exposure to ethoprop residues have been conducted by DPR. The acute and annual dietary exposure to primary residues on raw agricultural commodities (RAC) and secondary residues, which result from residues on animal feeds, have been assessed under the provisions of AB2161 (Food Safety Act). No measurable residues of ethoprop were detected on any commodity. The theoretical exposure to tolerance level residues in RAC as might be consumed by members of specific population subgroups, including infants and small children, and the attendant risks have been assessed. The population subgroup, non nursing infants less than 1 year of age had the highest theoretical acute dietary exposure to ethoprop. Children (1-6 years) had the highest theoretical annual exposure.

RISK EVALUATION

For work tasks associated with the EC formulation except for irrigators of fields, the margins of safety (MOSs), based on a NOEL for cholinergic signs and death in rabbits, for mean short-term occupational exposures to ethoprop were less than 100, the value conventionally recommended to protect people from the toxic effects of a chemical. MOSs for the 95th percentile of exposure of loader/applicator/incorporators using the 5G and 10G formulations were less than 100, the value conventionally recommended to protect people from the toxic effects of a chemical. The MOSs for annual occupational exposure were greater than 100 for only the EC irrigators and loader/applicator/incorporators handling the 10G formulation.

The MOSs for all population subgroups from theoretical acute dietary exposure to ethoprop were greater than 100. The MOSs, based on a NOEL for hepatotoxicity in dogs, for theoretical annual dietary exposure to ethoprop were also greater than 100.

A tolerance assessment in which residues of ethoprop were equal to established USEPA tolerance values indicated that all population subgroups had MOSs greater than 100 for acute dietary exposure. Combining dietary and occupational exposure did not significantly alter the MOSs.

CONCLUSIONS

The MOSs for acute occupational exposures of mixer/loader/applicators and incorporators using the EC formulation, and loader/applicator/incorporators using the 5G and 10 G formulations of ethoprop were less than 100, the value conventionally recommended to protect people from the toxic effects of a chemical. Mixer/loader/applicators and incorporators using the EC formulation, and loader/applicator/incorporators using the 5G formulation had MOSs for potential annual occupational exposure which were less than 100. Incorporators using the EC formulation had an added lifetime risk of cancer ranging from 6.2×10^{-5} (maximum likelihood estimate) to 1.4×10^{-4} (95% upper bound).

Based on the available toxicity and residue data, DPR concludes that the margins of safety for theoretical acute dietary exposure to ethoprop residues on labeled use foodstuffs are greater than 100. Margins of safety for theoretical annual dietary exposure are also greater than 100 for all population subgroups. The USEPA tolerances for ethoprop on agricultural commodities provide adequate margins of safety for theoretical acute exposure.

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I. SUMMARY

Ethoprop is a restricted, organophosphate pesticide which acts in animals by the inhibition of the enzyme cholinesterase (ChE). It is used in agriculture as an insecticide, nematicide and fungicide on food and non-food crops. The latest use figures in California (1991) indicate an annual use of 77,274 pounds mostly on potatoes (97.2%). Ethoprop entered the risk assessment process due to its high acute toxicity, possible oncogenicity, and adverse effects on the liver caused by chronic exposure.

Environmental Fate- Ethoprop does not strongly adsorb to soils, and field studies demonstrated moderate to high mobility potential in the soil. Under high rainfall conditions, ethoprop has the potential to contaminate shallow ground water. It slowly hydrolyzes under acidic, basic or neutral pH. The major mechanism of dissipation for ethoprop in soils is degradation through microbial metabolism. Ethoprop taken up by the root system of plants was extensively metabolized. Apparently as a consequence of rapid metabolism, ethoprop residues have not been detected in plants.

Pharmacokinetics- The half-life of ethoprop in the rat ranges from 91 to 134 hours. Neither ethoprop nor its metabolites accumulated in tissues after multiple doses through the oral route. The principal excretion routes following oral administration were via the urine (50-59%), expired air (11-19%), and feces (10-16%). The comparable excretion pattern following oral or intravenous administration of ethoprop suggests that absorption by the oral route is at least 90% of the administered dose.

Acute Toxicity- Ethoprop is highly toxic to experimental animals by all routes of exposure. It is particularly toxic to rabbits by the dermal route (LD_{50} is 24 mg/kg). The oral LD_{50} is 61 mg/kg in male rats, and 33 mg/kg in female rats. Clinical signs of acute toxicity are characteristic of cholinesterase inhibition and include salivation, lacrimation, irregular breathing, ataxia, tremors and convulsions followed by death if recovery does not occur.

Subchronic Toxicity- The principal effects of short-term exposure to ethoprop were related to inhibition of cholinesterase activity. The 1-week, oral Lowest-Observed Effect Level (LOEL) for inhibition of serum, red blood cell and brain ChE activity in mice was 15 mg/kg-day. The 1-week No-Observed Effect Level (NOEL) for cholinergic signs (tremors, decreased defecation, hunched posture labored breathing, and anogenital staining) was 15 mg/kg-day for dietary exposure to mice. In dogs, the 4-week, oral NOEL for inhibition of plasma cholinesterase activity was 0.01 mg/kg-day. The 1-day dermal NOEL in rabbits for clinical signs was 0.7 mg/kg. The 3-week dermal NOEL in rabbits was 0.07 mg/kg-day for inhibition of serum, brain, and red blood cell cholinesterase activity.

Chronic Toxicity- The principal non-oncogenic effects resulting from chronic exposure to ethoprop were hepatotoxicity, reduction of hematopoetic function, and inhibition of cholinesterase activity. In dogs, the LOEL for hepatotoxicity (elevated SGPT and alkaline phosphatase, centrilobular vacuolation, focal necrosis, periportal fibrosis and biliary proliferation) was 1 mg/kg-day, with a NOEL of 0.025 mg/kg-day. The NOEL for effects on the hematopoetic system (reduced red blood cell counts, decreased hemoglobin levels, and reduced hematocrit) in dogs was 1 mg/kg-day. Male mice exhibited preneoplastic hepatocellular lesions (hyperplastic nodules and foci of cellular alterations), with a NOEL of 4.9 mg/kg-day. The NOEL for inhibition of plasma, red blood cell and brain cholinesterase activity in the mouse was 0.3 mg/kg-day. The NOEL for inhibition of brain ChE activity in rats was 0.05 mg/kg-day. Ethoprop was not oncogenic in mice. However, oncogenicity in rats was indicated

by a statistically significant increase in malignant pheochromocytomas of the adrenal glands of males, but not females at the high dose. Females exhibited a significant increase in endometrial stromal polyps at the high dose.

Genotoxicity- Ethoprop was not mutagenic in *in vitro* eukaryotic and microbial tests. Ethoprop did not induce unscheduled DNA synthesis in rat hepatocytes and did not increase the mutation frequency in mouse lymphoma and Chinese hamster ovary cells. No chromosomal aberrations were observed in the bone marrow cells of rats treated with ethoprop. However, positive effects were observed in the SCE assay and a chromosomal aberration test using Chinese hamster ovary cells *in vitro*. A dominant lethal assay conducted in rats also showed positive results. Ethoprop is considered to have genotoxic potential.

Reproductive Toxicity- Ethoprop was not associated with specific reproductive effects in the rat. It did cause decreased mean birth weights of pups (F_{1a}, F_{1b}), a decrement in weight gain (F_{1a}, F_{1b}, F_2), and decreased weanling survival (F_{1a}) in rats. The LOEL for these effects was 7.1 mg/kg-day, with a NOEL of 1.7 mg/kg-day. The NOEL for inhibition of brain cholinesterase activity was 0.09 mg/kg-day.

Developmental Toxicity- Ethoprop was not teratogenic in rats or rabbits. The main effects noted in developmental toxicity studies were associated with inhibition of cholinesterase activity. In rats, the LOEL for maternal toxicity (clinical signs) was 18 mg/kg-day with a 2-day NOEL of 9 mg/kg-day. The LOEL for maternal toxicity (reduced body weight gain and death) in an earlier rat study was 16 mg/kg-day with a NOEL of 1.6 mg/kg-day. In rabbits, the LOEL for maternal toxicity (cholinergic signs and death) was 5.0 mg/kg-day with a 2-day NOEL of 2.0 mg/kg-day. In a different rabbit study, the NOEL for decrement in maternal weight gain (14%) was 0.125 mg/kg-day (LOEL = 0.5 mg/kg-day).

Neurotoxicity- Ethoprop caused no clinical signs of delayed neurotoxicity (locomotor ataxia), and no histopathological evidence of nerve damage in hens. In rats, the single dose NOEL for cholinergic signs, reduced motor activity, and reduced scores on the functional observational battery was 5 mg/kg. The 4-week NOEL for clinical signs and decreased performance on the functional observational battery in rats was 3.0 mg/kg-day. A single dose of ethoprop produced significant reduction in brain cholinesterase activity which persisted for up to 15 days.

Hazard Identification- A NOEL of 2 mg/kg-day for maternal toxicity in rabbits (cholinergic signs and death) was used to assess the margins of safety for potential acute exposures to ethoprop. The NOEL, 0.025 mg/kg-day, for hepatotoxicity (centrilobular vacuolation, focal necrosis, periportal fibrosis and/or biliary proliferation in the liver) in dogs was used to calculate margins of safety for potential annual exposures to ethoprop. Because the weight of evidence suggests that ethoprop has oncogenic potential, a quantitative risk assessment, based on the incidence of malignant pheochromocytomas, was conducted. The maximum likelihood estimate (q_1) of the potency was 2.8×10^{-2}., with an upper bound (q_1*) of 6.5×10^{-2}.

Dietary Exposure- Reported food residues were below the MDL and the tolerance levels. Based on the 95% percentile of user-days exposures for all specific population subgroups, the theoretical acute dietary exposure of ethoprop from all labeled uses ranged from 0.13 (females, 13 years and older/pregnant/not nursing) to 0.60 (non-nursing infants) *u*g/kg-day. The mean theoretical annual dietary exposure for all population subgroups ranged from 0.03 (nursing infants less than 1 year) to 0.09 (children 1-6 years old) *u*g/kg-day.

Occupational Exposure- The primary occupational exposure to ethoprop is via the dermal route, and to a much lesser extent through inhalation. Exposure estimates for the various occupational categories were based on actual monitoring data, and calculations from monitoring data for surrogate active ingredients with similar application rates and chemical properties. Mean Absorbed Daily Dosages (ADD) ranged from 0.2 *u*g/kg for irrigators to 139 *u*g/kg for incorporators working with the EC formulation. Annualized Average Daily Dosages (AADD) ranged from 0.01 *u*g/kg for irrigators, to 3.8 *u*g/kg for incorporators using the EC formulation. Combined theoretical acute dietary and occupational exposures ranged from 0.3 to 139 *u*g/kg. Under annual exposure conditions, the combined exposures ranged from 0.04 (irrigators) to 3.83 *u*g/kg-day (incorporators).

Risk Characterization- The margins of safety for potential mean acute exposure ranged from 14 for incorporators using the EC formulation to 10,000 for the irrigators. Even though all workers included in exposure studies wear the required protective gear, there is a range of exposures. The 95th percentile of short-term exposure was used to indicate the high end of worker exposures. If the 95th percentile of short-term exposure [geometric mean x (standard deviation)$^{1.645}$] were considered for workers using the 5G and 10G formulations, the MOSs would be 29 and 40, respectively. The margins of safety for annual occupational exposure ranged from 7 for incorporators using the EC formulation to 2,500 for irrigators. The added risk of cancer from lifetime exposure to ethoprop, based on the maximum likelihood estimate (MLE), ranged from 1.7 x 10^{-7} for irrigators using the EC formulation to 6.2 x 10^{-5} for incorporators. The 95% upper confidence limit on the added risk of cancer from lifetime exposure to ethoprop ranged from 3.9 x 10^{-7} for irrigators using the EC formulation to 1.4 x 10^{-4} for incorporators. The MOSs for theoretical acute dietary exposure to ethoprop for all population subgroups at the 95th percentile ranged from 3,000 for non-nursing infants (less than 1 year) to 15,000 for females (13 years and older/pregnant/not nursing). The MOSs for theoretical annual dietary exposure to ethoprop for all population subgroups ranged from 300 for children (1-6 years) to 1,000 for nursing infants (less than 1 year old).

Conclusions- Using the EC formulation, only irrigators had a MOS for acute exposure to ethoprop that was greater than 100, the value conventionally recommended to protect people from the toxic effects of a chemical. MOSs for mean acute exposure of loader/applicator/incorporators using either the 5G or 10G formulation were greater than 100. MOSs for the 95th percentile of short-term worker exposure for loader/applicator/ incorporators using either the 5G or 10G formulation were less than 100. Under the annual exposure conditions, only EC formulation irrigators and 10G loaders/applicators/ incorporators had MOSs that were greater than 100. The maximum likelihood estimate of added risk of cancer from lifetime exposure to ethoprop ranged from 1.7 x 10^{-7} for irrigators using the EC formulation to 6.2 x 10^{-5} for incorporators. The 95% upper confidence limit on the added risk of cancer from lifetime exposure to ethoprop ranged from 3.9 x 10^{-7} for irrigators using the EC formulation to 1.4 x 10^{-4} for incorporators.

Margins of safety for theoretical acute and annual dietary exposure to ethoprop by the general public were greater than 100. Tolerances for ethoprop on the most highly consumed commodities ranged from 7,000 to 220,000 for theoretical acute dietary exposure for all population subgroups.

II. INTRODUCTION

A. CHEMICAL IDENTIFICATION

Ethoprop (O-ethyl-S-S-dipropyl phosphorodithioate) is an organophosphate pesticide produced by Rhone-Poulenc. Ethoprop entered the risk assessment process due to its high acute toxicity, possible oncogenicity, and adverse effects on the liver caused by chronic exposure. Pesticidal activity of ethoprop is due to inhibition of acetylcholinesterase (AChE) activity. Cholinesterases are a family of enzymes found throughout the body that hydrolyze choline esters. In the nervous system, acetylcholinesterase is involved in the termination of impulses across nerve synapses including neuromuscular junctions by rapidly hydrolyzing the neural transmitter, acetylcholine. Inhibition of AChE leads to accumulation of acetylcholine in the synaptic cleft which results in over stimulation of the nerves followed by depression or paralysis of the cholinergic nerves throughout the central and peripheral nervous system. AChE is highly selective, although not exclusively, for acetyl esters as substrates (Brimijoin, 1992). Another form of cholinesterase, butyrylcholinesterase (BuChE), preferentially hydrolyzes butyryl and propionyl esters, depending on the species; however, it will hydrolyze a wider range of esters, including acetylcholine (Brimijoin, 1992). Unlike AChE, the physiological function of BuChE is not known. Although AChE and BuChE are found in most tissues, their ratio varies from one tissue to another and from one species to another. In rats, AChE is the predominant form of ChE in the central nervous system and in the neuromuscular junctions of peripheral tissues such as the diaphragm, skeletal muscle, heart, and spleen (Gupta *et al.*, 1991; Mendoza, 1976). AChE and BuChE are present in roughly equal proportions in the liver and kidney in young rats (Mendoza, 1976). Non-synaptic AChE is also present to a lesser extent in peripheral tissues; however, its function is not known (Brimijoin, 1992). Non-synaptic AChE is essentially the only ChE present in erythrocytes of higher animals. BuChE is the predominant form of ChE in the plasma of humans; however, the ratio of AChE to BuChE varies greatly from species to species and between sexes. For example, the AChE:BuChE ratio in human plasma is approximately 1:1000, but closer to 1:2 in female rats and 3:1 in male rats.

In acutely toxic episodes, muscarinic, and nicotinic receptors are stimulated by acetylcholine with characteristic signs and symptoms occurring throughout the peripheral and central nervous systems (Ellenhorn and Barceloux, 1988; Murphy, 1986). Peripheral muscarinic effects can include increased intestinal motility, bronchial constriction and increased bronchial secretions, bladder contraction, miosis, secretory gland stimulation and bradycardia. Peripheral nicotinic effects include muscle weakness, twitching, cramps and general fasciculations. Stimulation of muscarinic and nicotinic receptors in the central nervous system can cause headache, restlessness, insomnia, anxiety, slurred speech, tremors, ataxia, convulsions, depression of respiratory and circulatory centers, and coma. Death, which occurs in the worst circumstances, is usually due to respiratory failure from a combination of peripheral and central effects.

B. REGULATORY HISTORY

An Ethoprop Registration Standard was issued by the U. S. Environmental Protection Agency (USEPA) in 1983 (USEPA, 1988). In that Standard, data gaps were identified according to policies in place at that time. Registrants were notified of the required studies and the time frames for submitting data to the Agency. A Guidance for the Reregistration of Ethoprop was published by the USEPA in 1988 (USEPA, 1988). The reregistration Guidance retained the restricted use classification for the emulsifiable concentrate (EC) formulation containing over 40% active ingredient (a.i.). Granular formulations 10% and greater were

proposed for "Restricted Use" classification based on the "acute dermal toxicity and avian hazard". As of December, 1991, all information required for ethoprop by California Senate Bill 950 (The Birth Defect Prevention Act) had been submitted by Rhone-Poulenc.

The USEPA Office of Pesticide Programs lists a reference dose (RfD) of 0.000015 mg/kg-day, based on a NOEL of 0.015 mg/kg-day for decreased weight of adrenal glands, and inhibition of red blood cell and brain cholinesterase activity in female rats in a 90 day feeding study (USEPA, 1993). The World Health Organization (WHO) RfD is 0.0003 mg/kg-day (USEPA, 1993).

C. TECHNICAL AND PRODUCT FORMULATIONS

There are presently three formulations containing ethoprop registered for use in California: Mocap® EC, Mocap® 10G, and Chipco Mocap® 5% Granular. Mocap® EC is an emulsifiable concentrate containing approximately 70% of the a.i. The labels on these formulations carry "Restricted Use Pesticide" classification intended "for retail sale to, and use by certified applicators or persons under the direct supervision of a certified applicator, and only for those uses covered by the certified applicators certification".

The label for Mocap® 10G and Chipco MOCAP 5G carries a "Warning" signal word and that for MOCAP EC has a "Danger" signal word. Protective clothing, including rubber gloves, is required for applying Mocap® 10G and Chipco Mocap® 5G. Application of Mocap® 10G also requires wearing a mask or pesticide respirator jointly approved by the Mining Enforcement and Safety Administration and the National Institute for Occupational Safety and Health. The application of Mocap® EC requires wearing waterproof protective clothing, rubber gloves, goggles, and an AO R-6058 respirator with a R-58 cartridge or equivalent for protection during field handling and field exposure.

D. USAGE

Ethoprop is used as an insecticide, nematicide and fungicide (suppression of white mold on peanuts) on food and non-food crops (USEPA, 1988). The active ingredient must be mixed with soil or carried into soil by water to be effective. All applications must be mechanically incorporated and/or watered into the soil primarily from overhead irrigation (Appendix A). After application, reentry by field workers or others into treated areas is prohibited in California until the product has been incorporated into the soil. The incorporator must wear the same personal protective equipment as application personnel (Appendix A). The application rate ranges from 2 to 16 lbs a.i./acre for Mocap® EC, 5 to 30 lbs a.i./acre for Chipco Mocap® 5G, 2 to 10 lbs a.i./acre for Mocap® 10G.

Approved usages listed on California registered labels are:
Mocap® EC: banana/plantain, bean (snap and lima), cabbage, citrus seedlings, corn (field and sweet), cucumber, peanuts, pineapple, potatoes (white and sweet), soybeans, sugarcane, and tobacco.
Mocap® 10G: cabbage, corn (field and sweet), cucumber, peanuts, potatoes, soybeans, sugarcane, sweet potatoes, and tobacco.
Chipco Mocap® 5G: turf grass (home lawns and commercial turf).

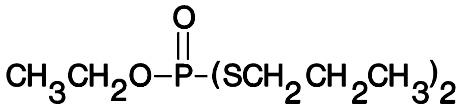
In 1993, 62,143 pounds (28,250 kg) of the active ingredient were used in California (DPR, 1995). The DPR Use Report indicated that the majority (97.2%) of ethoprop used in California was applied to potatoes, sweet potatoes, cabbage and beans.

E. ILLNESS REPORTS

From 1981 through 1988, no occupational illnesses or injuries involving ethoprop were reported. In 1989, there were ten reported cases "possibly" associated with ethoprop exposure (nine cases involving systemic effects and one involving eye injury) and one systemic case classified as "definite/probable" (Mehler, 1991). One epidemiological report indicated that *n*-propyl mercaptan, a contaminant and breakdown product of ethoprop, may have caused headaches, diarrhea, sore throats, fever, burning/itching eyes, asthma attacks, and hay fever attacks in a rural California population (5 complainants) near a treated potato field in 1989 (Ames and Stratton, 1991). However, no air monitoring samples were collected, and the survey was conducted six weeks after the pesticide had been applied.

F. PHYSICAL and CHEMICAL PROPERTIES[a]

Chemical Name:	O-ethyl S,S-dipropyl phosphorodithioate
Common Name:	ethoprophos, ethoprop
Trade Names:	Mocap®,
Empirical Formula:	$C_8H_{19}O_2PS_2$
Structural Formula:	



Molecular Weight:	242.3 g/mole
Boiling point:	86-91°C (at 0.2 mm Hg)
Vapor pressure:	0.00035 mm Hg (at 26°C)
Specific gravity:	1.094
Solubility:	Very soluble in most organic solvents Soluble to 843 ppm in water at 21°C
Octanol/water K_{ow}:	3900
Physical appearance:	Clear pale yellowish liquid with strong mercaptan odor
Stability:	Relatively stable in neutral and acidic media; hydrolyzes more rapidly in basic media; thermally stable at 50°C for at least 12 weeks; stable to sunlight.

a/ Reference: Rhone-Poulenc Inc. 1986.

G. ENVIRONMENTAL FATE

Summary. Ethoprop does not strongly adsorb to soils, and field studies demonstrated moderate to high mobility potential in the soil. Under high rainfall conditions, ethoprop has the potential to contaminate shallow ground water. It slowly hydrolyzes under acidic, basic or neutral pH. The major mechanism of dissipation for ethoprop in soils is degradation through microbial metabolism. Ethoprop was taken up by the root system of plants and extensively metabolized. Apparently as a consequence of rapid metabolism, ethoprop residues were not detected in plants.

Hydrolysis

Ethoprop was relatively stable at pH 3 to pH 7 (Das, 1989). The hydrolysis rate was slowest at pH 3 with a half-life ranging from 16 to 36 weeks depending on the temperature. The half-life of ethoprop decreased as the temperature increased. At pH 9, the half-life of ethoprop was 83 days. The two major degradation products identified were ethyl alcohol and S,S-dipropyl phosphorodithioate.

The stability of [^{14}C-propyl]-ethoprop (2 *u*g/ml) in aqueous buffered solutions (pH 3, 6, and 9) was monitored for six weeks in sealed vessels in the dark at 20^{o}C or 35^{o}C (Norris, 1983a). At 20^{o}C, the half-lives of 2 *u*g/ml buffered solutions were 28, 33, and 6.3 weeks, at pH 3, 6 and 9 respectively. At 35^{o}C, the half-lives of 2 *u*g/ml buffered solutions were 16, 14, and 1.5 weeks, at pH 3, 6 and 9 respectively.

Photodegradation

[^{14}C-ethyl]-Ethoprop (22.4 *u*g/ml) was incubated at 25^{o}C in a sterile, aqueous, buffered solution (pH 7) for a 30 day period (Carpenter, 1989). The exposed samples were subjected to continuous irradiation of a xenon arc lamp at approximately 50% the intensity of sunlight. An estimate of the half-life for photolysis could not be obtained due to the lack of significant degradation. Accountability for ^{14}C-activity for the study ranged from 98.4 to 106%.

Artificial irradiation (300-400 nm in a Rayonet Photochemic Chamber Reactor with RPR-2000A^{o} and RPR-3500A^{o} lights) of [^{14}C-propyl]-ethoprop aqueous solution resulted in first order decline of ethoprop, with a half-life of 75 days. Under photosensitized conditions (2% acetone, v/v) it degraded faster with a half-life of 24 days (Norris, 1983b). There was no degradation under dark conditions. The polar degradation product was presumed to be O-ethyl-S-propyl phosphorothioic acid.

The degradation of [^{14}C-propyl]-ethoprop (14 ppm) on layers of a sandy loam soil was accelerated by simulated sunlight in a Rayonet Photochemic Chamber Reactor with RPR-2000A^{o} and RPR-3500A^{o} lights (Cresswell and Hopkins, 1986). The half-lives of ethoprop in irradiated and unirradiated samples were calculated to be 14 and 37 days, respectively. After 15 days, soil-bound radioactivity in the unirradiated and irradiated samples accounted for 15.3% and 28.5% of the applied radioactivity, respectively. Approximately 7% of the applied radioactivity was presumed to have evolved as carbon dioxide.

Microbial Degradation

The metabolism of [^{14}C-propyl]-ethoprop was investigated in sandy clay and sandy loam soils incubated aerobically at a temperature of 22^{o}C or 10^{o}C (Greensdale *et al*, 1984). At 22^{o}C, degradation half-lives for the sandy clay loam and sandy loam soils were 24.8 and 24.1 days, respectively. Evolution of $^{14}CO_2$ accounted for approximately 56-60% of the applied radioactivity within 90 days of treatment. Unchanged ethoprop accounted for 7 to 9%. Trace products (0.1-0.5%) were detected, corresponding in Rf values to ethylpropylsulphoxide and ethylpropylsulfone. At 10^{o}C, degradation half-lives in the sandy clay loam and sandy loam soils were 43.4 and 41.8 days, respectively. Approximately 43 to 50% of the applied radioactivity was recovered as $^{14}CO_2$ within 110 days of treatment.

Microbial activity enhances degradation of ethoprop in soils (Smelt *et al*, 1987). The half-life of ethoprop in autoclaved soil (no living microbes) was 408 days. The half-life of ethoprop in unautoclaved soil taken from plots previously treated with ethoprop was 5 days.

Another metabolism study of [^{14}C-ethyl]-ethoprop was conducted in a loamy sand soil maintained at a moisture content of 6.1% and incubated at 25^{o}C in darkness (Jordan, 1986). In this study, the major degradation product was $^{14}CO_2$, accounting for 54% of the applied ethoprop after 252 days under aerobic conditions. The fate of ethoprop was also investigated under anaerobic conditions for 56 days, following initial aerobic incubation in soil (28 days). The amount of $^{14}CO_2$ recovered under the anaerobic conditions was approximately 3% after 56 days of treatment. The major residual metabolite in soil was O-ethyl-S-propylphosphorothioic acid. Two minor metabolites, O-ethyl-O-methyl-S-propylphosphorothioate and O-ethyl-S-methyl-S-propylphosphorodithioate also were identified. The accumulation of these metabolites under anaerobic conditions was minimal. The half-lives of ethoprop were 100 and 130 days under the aerobic and anaerobic conditions of the study, respectively.

Mobility in Soil

Laboratory studies employing [^{14}C-ethyl]-ethoprop have shown that ethoprop is not strongly adsorbed to soils (Jordan, 1985). Adsorption coefficients (K_{oc} values) ranged from 112 to 186 in four soil types- sandy loam (1% organic matter), sandy loam (2% organic matter), silt loam (2.3% organic matter), and silty clay loam (4.1% organic matter). The desorption of ethoprop in these soils ranged from 215 to 1286. These results suggest medium to high potential mobility for ethoprop in soils ranging from sandy loam to silty clay.

An earlier field experiment (Rohde *et al*, 1979) showed that the formulation of Mocap® influenced the persistence of ethoprop in soil. Both the concentration and the persistence of ethoprop in the top 10 cm of soil were higher following application of the 10G formulation (10% a.i.) compared to the 6L formulation (2.7 kg a.i./L). Conversely, 2-3 days after application, a higher concentration of ethoprop was found in runoff water following application of the liquid formulation.

A study of the field dissipation of ethoprop in four different states (Missouri, Illinois, New Jersey, Nebraska) was submitted to DPR (Guyton, 1986). The organic content of the soils ranged from 1.7 to 5.4%, and the weather conditions ranged from little rainfall (0.37 in.) to sufficient rainfall (4.35 in.) for the first 30 days of the study. Ethoprop residues were analyzed only from the top 12 inches of the soil and seemed to be concentrated in the top 6 inches. Extreme fluctuations in the ethoprop residues found in the soil from month to month, and lack of residue analysis below 12 inches made it difficult to reach a definite conclusion regarding vertical movement.

Field dissipation of ethoprop was reported in another study conducted in California (Norris, 1990a). Mocap® 10G was applied to a loam soil (pH 7.9-8.5; organic matter 0.6-1.5%) under standard agricultural practices. Ethoprop residues were detected throughout a 35 inch soil profile for up to one month after application (70 ppb at 35 inches depth). The half-life of ethoprop dissipation under these conditions was calculated to be 23.3 days. Other field dissipation studies conducted in North Carolina and Washington showed ethoprop residues moved to a depth of 24-35 inches during the first month after application (Norris, 1990b).

Weaver *et al*. (1988) investigated the leaching potential of ethoprop in two counties (Humboldt and Siskayou) in Northwestern California under heavy rainfall conditions. Ethoprop was applied in liquid (Mocap® 70% liquid at 2 quarts/acre) or granular formulation (Mocap® 10G, 30 gm/22 ft over 10-inch band). Leaching occurred in spite of relatively high (2.5-6.6%) organic matter contents in the top foot of soil. Ethoprop persisted for 8 months in soil and leached to a depth of 48-54 inches following a total rainfall of 37 to 50 inches. Concentrations of ethoprop found in soil below 30 inches ranged from 0.01 to 0.07 ppm. The results indicated that, under conditions of high rainfall, ethoprop might contaminate shallow ground water.

Plant Metabolism

The metabolism of ethoprop in bean and corn plants was studied by applying Mocap® 10% granules spiked with [^{14}C]-ethoprop to the soil (Menzer *et al*., 1971). Uptake of ethoprop by the plants was slow. Considering the specific activity of the a.i., 7 to 9% of the applied ethoprop was recovered in bean plants 63 days after the treatment. Approximately 34-71% was recovered in corn plants 100 days after the treatment. The organic extracts of bean and corn plants contained ethyl propyl sulfide, ethyl propyl sulfoxide, ethyl propyl sulfone, and propyl disulfide. The major water-soluble metabolite isolated from plants was O-ethyl-S-propyl phosphorothioic acid.

[^{14}C-ethyl]-Ethoprop applied to the soil in an emulsifiable form was absorbed and extensively metabolized by crops (Johnson, 1990 and 1991a,b). In one field test, cabbage plants were grown in a ^{14}C-ethoprop treated soil at the rate of 10 lbs a.i./acre. Total ^{14}C residues in the leafy and head cabbage were 15.6 and 3.1 ppm of ethoprop equivalents, respectively. Ethyl phosphate was the major metabolite (more than 20% of the total radioactivity). O-ethyl-S-propylphosphorothioate, O-ethyl-S-methyl-S-propylphosphorodithioate, O-ethyl-O-methyl-S-propylphosphorothioate (0.07-0.36 ppm for both) and parent ethoprop (0.025-0.634 ppm) were detected in addition to six other unidentified metabolites. A second field test was conducted with corn grown in soil treated with ^{14}C-ethoprop at 12 lbs a.i./acre. Total radioactivity detected in the corn forage, cobs, grain, husks, and fodder was 2.18, 0.27, 0.25, 0.79, and 1.42 ppm ethoprop equivalents, respectively. Ethoprop was detected in the forage (0.17 ppm) and in the fodder (0.01 ppm). A third test was conducted using potatoes grown in ^{14}C-ethoprop treated soil at 12 lbs a.i./acre (15.2 ppm). Analysis of potato vines and tubers showed a concentration of 1.11 and 0.54 ppm ^{14}C equivalents, respectively. Qualitatively the metabolism of ethoprop was similar in the three crops. Ethyl phosphate was the major terminal residue. Numerous unidentified products, thought to be ^{14}C-label incorporated into natural plant constituents, were also reported.

Residues

Results of field tests indicate that most crops grown in soils treated with ethoprop have non-detectable residues (minimum detection limit, MDL, = 0.01 ppm) (Guyton, 1985). Broccoli and cauliflower grown in soil treated with Mocap® 6EC at 12 lb a.i./acre had <0.01 ppm 64-135 days after treatment from sites in California, Georgia, New Jersey and Oregon.

In another field test in California, ethoprop was applied to grape vineyards soils at the rate of 12 lb a.i./acre. Grapes, grape juice, grape pomace and raisins analyzed from this treated vineyard contained no detectable (MDL $\leq$0.02 ppm) ethoprop residues 35-63 days after application (Guyton, 1982). Corn grown in soil treated with Mocap® EC at the rate of 1-9 lb a.i./acre had no detectable residues (MDL $\leq$0.02 ppm) in the grain, stalks, silage, fodder or the ears after 64 to 184 days (Kanuk, 1976)

No ethoprop residues were detected in beet, cabbage, cantaloupe, peas or tomatoes grown in soils treated with Mocap® 10G at 3.4-13.4 kg/ha (Argauer and Feldmesser, 1978). However, residues were reported in onions (0.12, 0.52, and 1.3 ppm) and radishes (0.12, 0.33 and 0.66 ppm) at 3.4, 6.7, and 13.4 kg/ha application rates of Mocap® 10G, respectively.

Snap beans, tomatoes, cucumber and lettuce grown in soil treated with Mocap® 10G at 3.4, 6.7 or 13.4 kg/ha and harvested at 58 to 108 days post-application, had residues <0.005 ppm except for beans with 0.018 ppm reported at the highest rate of application (Hunt *et al*, 1981). However, the root crops all had measurable residues at all the application rates- onion (0.009 - 0.068 ppm), turnip roots and leaves (0.001 - 0.281 ppm), and radish (0.018 - 0.345 ppm). The ethoprop residues were proportionate to the application rate.

Tolerances are presently established at 0.02 ppm for residues of ethoprop on all agricultural commodities (CFR 40; Appendix B). There are no international tolerances or CODEX Maximum Residue Limits for residues of ethoprop.

III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS

Summary. The half-life of ethoprop in the rat ranges from 91 to 134 hours. Neither ethoprop nor its metabolites accumulated in tissues after multiple doses through the oral route. The principal excretion routes following oral administration were via the urine (50-59%), expired air (11-19%), and feces (10-16%). The comparable excretion pattern following oral or intravenous administration of ethoprop suggests that absorption by the oral route is greater than 90% of the administered dose.

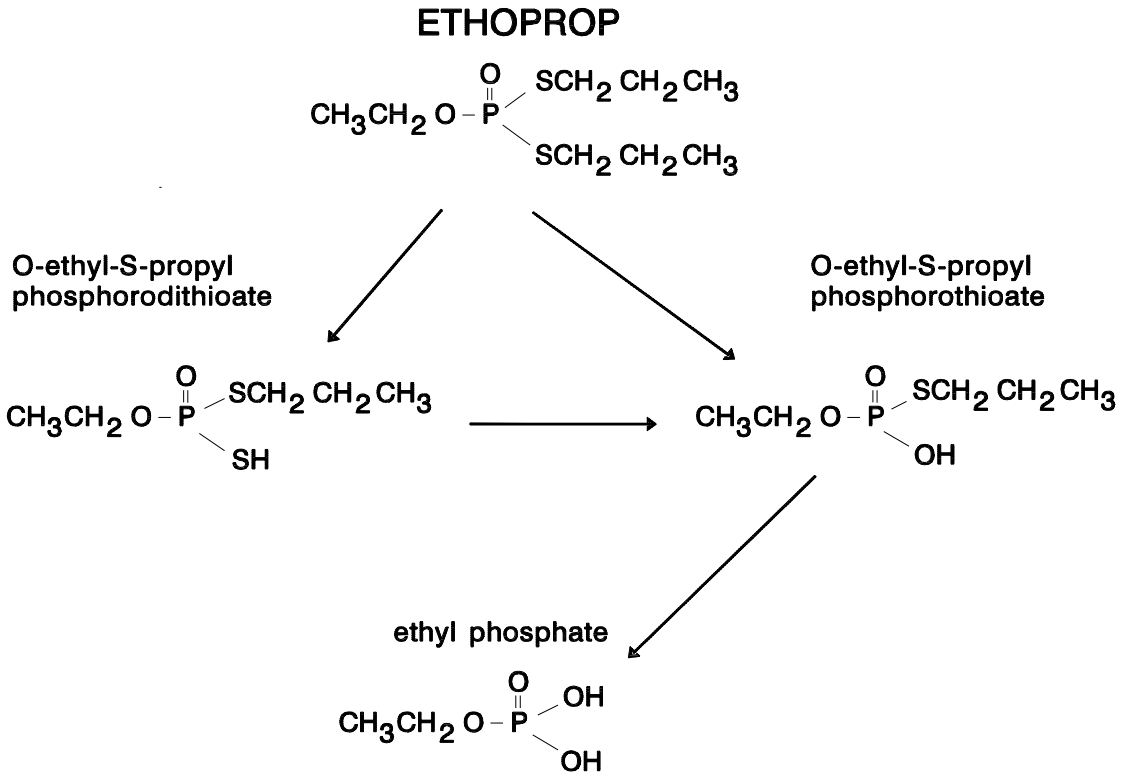
Oral and Intravenous- Rat

Ethoprop (ethyl-1-^{14}C; 97% purity) was administered to male and female rats in a single intravenous dose (4 mg/kg), a single oral dose (4, 12.5, or 25 mg/kg), or multiple oral doses (4 mg/kg-day) for 15 days (Yenne, 1990). Following oral dosing, the maximum blood concentration (C_{max}) was rapidly attained, with a time to reach C_{max} of 0.5 to 0.7 hour. Thereafter, concentrations of radioactivity declined in a multi-exponential manner. The mean terminal half-life was 91 to 134 hours. Metabolism and excretion of ethoprop were independent of sex, route of administration, dose level, and dose frequency. Primary routes of excretion following oral administration were via the urine (50-59% of administered radiolabel), expired air (11-19% of administered radiolabel), and feces (10-16% of administered radiolabel). Excretion following intravenous administration via the urine, expired air, and feces was approximately 57%, 15%, 8% of administered radiolabel, respectively. The comparable excretion pattern following oral or intravenous administration of ethoprop suggests that absorption by the oral route is greater than 90% of the administered dose. Residual radioactivity in tissues was low (0.3-3%) and primarily detected in organs associated with metabolism and excretion (i.e. liver, kidney, and lung). There was no evidence to suggest that ethoprop and/or its metabolites accumulated in tissues after multiple dosing. The proposed metabolic pathway for ethoprop in rats is depicted in Figure 1.

Oral- Rat

Ethoprop (^{14}C-ethyl, S.A. 1.25 mCi/mmole; or ^{14}C-propyl, S.A. 2.8 mCi/mmole) at 1 or 3 x 10^6 cpm/min was administered by oral gavage to Sprague-Dawley rats (3/sex/isotope) in 0.25 ml of distilled water (Iqbal and Menzer, 1972). The major water soluble metabolite isolated from rat urine, liver microsomes, and supernatant was O-ethyl-S-propyl phosphorothioate. Rat urine also contained O-ethyl phosphoric acid, S-propyl phosphorothioate and S,S-dipropyl phosphorodithioate. The proposed metabolic pathway for ethoprop was the same as illustrated in Figure 1.

Figure 1. Proposed metabolic pathway for ethoprop in the rat. Both ethyl phosphate and O-ethyl-S-propyl phosphorothioate can also be excreted as conjugates in the urine and feces.



Dermal- Multiple Species

An *in vitro* skin penetration study of [^{14}C]-ethoprop emulsified concentrate in humans, mice, rats and rabbits was reported by Stoughton (1986). Dilute ethoprop formulation consistently penetrated skin 2 to 5-fold faster than the emulsified concentrate (Table 1). Some of the label passed through the skin to the solution on the other side, while some of the label remained in the skin. The penetration rate was lower with human skin than with the skin of other species. *In vitro* dermal penetration of human skin ranged from 6 to 19% of the rate measured for rats *in vitro*. *In vivo* dermal absorption data in humans or experimental animals were lacking. Consequently, a default value of 100% for dermal absorption was used for the purposes of this risk assessment.

Table 1 - *In vitro* skin penetration: Percent of dermally applied [^{14}C]-ethoprop in skin and/or passed through the skin (Stoughton, 1986).

	Emulsified Concentrate			Diluted Emulsion[a]		
Skin Source	4 hr[b]	6 hr	24 hr	4 hr	6 hr	24 hr
Human	<0.1	0.1	1.0	0.7	1.1	5.2
Mouse	2.6	5.0	16.2	11.0	29.0	37.8
Rabbit	0.7	1.5	7.8	3.7	7.7	27.4
Rat	1.0	1.7	5.4	4.2	7.9	22.7

a/ One part of emulsion concentrate was diluted with 19 parts of distilled water.
b/ Duration of application.

B. ACUTE TOXICITY

Technical ethoprop was highly toxic to laboratory animals when administered orally, dermally, or via inhalation (Table 2). Signs of acute toxicity observed in animals exposed to ethoprop were indicative of the cholinesterase inhibition. Typical clinical signs of acute toxicity included salivation, lacrimation, irregular breathing, ataxia, tremors, and convulsions (Dudek, 1984; Smith, 1984a,b; Powers, 1965; Myers, 1986; Nachreiner, 1986).

Findings at the necropsy of animals acutely exposed to ethoprop via the oral route included hyperemia of stomach, black foci on glandular stomach, lobular pattern of liver, congested liver, and congested lung (Smith, 1984a). Similar findings (excessive masticatory movements, salivation, blinking, miosis, incoordination of limbs, rapid labored respiration, tremors, clonic and tonic convulsions, and death) were reported in animals exposed to ethoprop via the dermal and inhalation routes at high dosages (Smith, 1984b; Myers, 1986; Nachreiner, 1986), and for rabbits exposed via the eyes (Weir, 1965; Munson, 1980a).

Table 2 - Acute toxicity of ethoprop in laboratory animals

Species	Sex	Results	Reference
		TECHNICAL	
Oral LD_{50}			
Rat	M	61 (49-75) mg/kg	1
	F	33 (25-42) mg/kg	1
Dermal LD_{50}			
Rabbit		24 mg/kg	2
Inhalation LC_{50}			
Rat		0.12 mg/L	3
		Mocap® 6EC (70% a.i.)	
Oral LD_{50}			
Rat	M	46.7 (31.5-69.0) mg/kg	4
	F	15.9 (13.6-21.8) mg/kg	4
	M/F	40 mg/kg	5
Dermal LD_{50}			
Rat	M	369 (204-669) mg/kg	4
	F	166 (116-238) mg/kg	4
Rabbit		25 mg/kg	6
Inhalation LC_{50}			
Rat	M	0.86 (0.60-1.23) mg/L	7
	F	0.32 (0.14-0.72) mg/L	7
Eye Irritation			
Rabbit		Moderate	8
Skin Sensitization		Not a sensitizer	9
		Mocap® 10G (10% a.i.)	
Oral LD_{50}			
Rat	M	425 (404-443) mg/kg	10
	F	159 (115-207) mg/kg	10
Dermal LD_{50}			
Rabbit	M	271 mg/kg	11
	F	246 mg/kg	11
Inhalation LC_{50}			
Rat	M	0.742 (0.224-2.453) mg/L	12
	F	0.361 (0.095-1.363) mg/L	12
Eye Irritation			
Rabbit		Moderate	13
Skin Irritation			
Rabbit		Non-irritating	14

References- 1. Powers, 1965; 2. Powers, 1965; 3. USEPA, 1988; 4. Myers, 1986; 5. Terrel and Parke, 1977; 6. Saunders, 1972; 7. Nachreiner, 1986; 8. Munson, 1980a; 9. Myers and Christopher, 1986; 10. Munson, 1980c; 11. Smith, 1986c; 12. Nachreiner, 1985; 13. Smith, 1986e; 14. Munson, 1980b.

Table 2 (cont'd) - Acute toxicity of ethoprop in laboratory animals

Species	Sex	Results	Reference
		Mocap® 5G (5% a.i.)	
Oral LD_{50}			
Rat	M	1336 (1266-1411) mg/kg	12
	F	719 (579-892) mg/kg	12
Dermal LD_{50}			
Rabbit	M	383 (319-461) mg/kg	13
	F	396 (334-469) mg/kg	13
Inhalation LC_{50}			
Rat	M/F	4.65 mg/kg	14
Dermal Irritation			
Rabbit		minimally irritating	15
Eye Irritation			
Rabbit		mildly irritating	16

References- 12. Smith, 1984a; 13. Smith, 1984b; 14. Dudek, 1984; 15. Smith, 1986a; 16. Smith, 1986b;

Dermal-Rat

A single dose of Mocap® 6EC (69.9% purity) was applied to the clipped skin of male rats (3/dose) at 0, 10, 20, 40, 160, or 320 mg formulation/kg to determine the effect on cholinesterase activity in the serum, red blood cells, and brain (Morrow, 1984). Enzyme activity was measured 72 hours after the test solution was applied. Inhibition of brain cholinesterase activity was dose related, and significantly ($P<0.01$, Student t test) different from controls at doses of 20 mg formulation/kg (20%), 40 mg formulation/kg (34%), 160 mg formulation/kg (56%), and 320 mg formulation/kg (58%). The 1-day dermal No-Observed Effect Level (NOEL) for inhibition of brain cholinesterase activity was 10 mg formulation/kg, or 7 mg ethoprop/kg. Plasma cholinesterase activity appeared to be inhibited at all dosages. Red blood cell (RBC) cholinesterase activity was not affected. Clinical signs of severe anticholinesterase toxicity, including salivation, irregular respiration, prostration, and morbidity, were observed in animals at the highest dose of 320 mg/kg. The 1-day dermal NOEL for cholinergic signs was 160 mg formulation/kg, or 111.8 mg ethoprop/kg.

Technical ethoprop (95% purity) and Mocap® 6EC (68.6% ethoprop), was applied dermally to 25 cm^2 clipped areas on the backs of male albino rats in order to compare the effects of the formulations on inhibition of red blood cell cholinesterase activity (Knaak *et al.*, 1986). The ED_{50} values (50% inhibition of RBC cholinesterase activity compared to controls) were 161, and 147 *u*g a.i./cm^2 of skin being treated for 72 hours with technical ethoprop and Mocap® 6EC, respectively. Mocap® 6EC inhibited RBC cholinesterase activity to a greater extent than did technical ethoprop possibly due to the effect on the skin by inert ingredients present in the formulation. The effect of the test materials on other parameters was not reported.

Dermal- Rabbit

Male and female New Zealand white rabbits (4/dose) were dosed dermally with technical grade ethoprop (purity unstated) at 10, 31.6, 100 and 1,000 *u*l/kg body weight (Powers, 1965). All rabbits died at the top two doses; 3/4 rabbits died at 31.6 *u*l/kg; no animals died at 10 *u*l/kg (approximately equivalent to a dose 10 mg/kg). Rabbits in the low dose group did exhibit clinical signs, including depression, labored respiration, unsteadiness, tremors, diarrhea, and periods of hyper- and hypo-activity.

In a dermal LD_{50} study, male albino New Zealand rabbits (4/dose) were dosed with Mocap® 6EC (69.6% purity) at 12.5, 25 and 37.5 mg formulation/kg on shaved skin under a protective covering for 24 hours (Saunders, 1972). Commencing at 4 hours, animals at the two highest doses exhibited ataxia, depression, dilation of pupils, excessive salivation, and loss of the righting reflex. This was followed by collapse and death in all animals at 37.5 mg/kg and in one animal at 25 mg/kg. None of the animals at 12.5 mg/kg exhibited any cholinergic signs. The dermal NOEL for cholinergic signs was 12.5 mg formulation/kg, or 8.7 mg ethoprop/kg.

C. SUBCHRONIC TOXICITY

Summary. The principal effects of short-term exposure to ethoprop were related to inhibition of cholinesterase activity. The 1-week, oral Lowest-Observed Effect Level (LOEL) for inhibition of serum, red blood cell and brain ChE activity in mice was 15 mg/kg-day. The 1-week NOEL for cholinergic signs (tremors, decreased defecation, hunched posture labored breathing, and anogenital staining) was 15 mg/kg-day for dietary exposure to mice. In dogs, the 4-week, oral NOEL for inhibition of plasma cholinesterase activity was 0.01 mg/kg-day. The 1-day dermal NOEL in rabbits for clinical signs was 0.7 mg/kg. The 3-week dermal NOEL in rabbits was 0.07 mg/kg-day for inhibition of serum, brain, and red blood cell cholinesterase activity.

Dietary - Mouse

Ethoprop (95.9%) was administered to B6C3F1 mice (10/sex/group) in the diet at 0, 100, 200 or 400 ppm (approximately 0, 15, 30 or 60 mg/kg-day using a default conversion of 0.15 mg/ppm; Zielhuis and van der Kreek, 1979) for 6 weeks (McGee, 1988). At 60 mg/kg-day, all animals died or were terminated in a moribund condition during the first week. Three females in the 30 mg/kg-day group died during the first two weeks (two on day 7, 1 on day 14). At 6 weeks, brain cholinesterase activity was significantly inhibited ($p \leq 0.01$) at 15 mg/kg-day (37 and 41% for males and females, respectively) and 30 mg/kg-day (28 and 32% for males and females, respectively). Mean plasma ChE activity was inhibited 95% at the 15 and 30 mg/kg-day. Mean red blood cell ChE was depressed at both the 15 and 30 mg/kg-day doses (48% and 40% for males and females, respectively). Cholinergic signs (including tremors, decreased defecation, hunched posture labored breathing and yellow anogenital staining) at the 30 and 60 mg/kg-day levels appeared 1 to 2 weeks after treatment had begun. The NOEL for clinical signs was 15 mg/kg-day. The LOEL for inhibition of serum, red blood cell and brain ChE activity was 15 mg/kg-day. The study was unacceptable as a subchronic study under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) guidelines series 82-1 because the histopathological examinations of designated tissues were not performed, and there was a lack of clinical chemistry and hematology, and the duration of the study was not adequate (USEPA, 1984). The data were considered supplemental in helping to establish the pattern of inhibition of cholinesterase activity, and providing a basis for comparing the dose response for cholinergic signs in laboratory animals.

Capsule - Dog

Technical ethoprop (purity 95.6%) was administered daily in gelatin capsules at 0, 0.01, 0.025, or 1.0 mg/kg-day to beagle dogs (6/sex/group) for 20 weeks (Hamada, 1990). Plasma cholinesterase activity in females receiving the 0.025 mg/kg-day, and in males and females receiving 1.0 mg/kg-day was significantly inhibited ($p \leq 0.05$) with mean values ranging from 17-26% and 74-80%, respectively, at all sampling times. Red blood cell cholinesterase activity was inhibited on weeks 8 (20% compared to controls) and 12 (26% compared to controls) in males receiving 1.0 mg/kg-day. No significant inhibition of the brain ChE activity was observed at the end of the study. No other treatment related effects, including clinical signs, were reported. The NOEL for inhibition of plasma cholinesterase activity was 0.01 mg/kg-day. The NOEL for inhibition of red blood cell cholinesterase was 0.025 mg/kg-day. The data were considered supplemental in helping to establish the pattern of inhibition of cholinesterase activity, and providing a basis for comparing the dose response for cholinergic signs in laboratory animals.

Dermal- Rabbit

Technical ethoprop (95.6% purity) was applied to intact, furless skin (approximately 10% of the total body surface on the dorsal trunk) of Hra:(NZW)SPF rabbits (10/sex/group) at 0, 0.02, 0.07, or 0.70 mg/kg-day (based on actual dose) for 6 hours/day, 5 days/week for at least 3 weeks (Henwood, 1989). No clinical signs were reported in the first week; therefore, the 1-day dermal NOEL for clinical signs was 0.7 mg/kg (the highest dose tested). At 0.02 mg/kg-day, one male and one female were terminated in moribund condition (days 13 and 19, respectively), and one female was found dead (day 19). Two males at 0.70 mg/kg-day were terminated in a moribund condition (days 14 and 20). There was an increased incidence of slight to moderate dermal irritation in all treated animals; the frequency of these incidences increasing with dosage. Significant (≤ 0.05) inhibition of plasma (35-37%), red blood cell (42%), and brain (49%) cholinesterase activity was observed at the high dosage of 0.70 mg/kg-day. The 3-week dermal NOEL was 0.07 mg/kg-day for inhibition of serum, brain, and red blood cell cholinesterase activity. The data were considered supplemental in helping to establish the pattern of inhibition of cholinesterase activity, and providing a basis for comparing the dose response for cholinergic signs in laboratory animals.

D. CHRONIC TOXICITY AND ONCOGENICITY

Summary. Ethoprop was not oncogenic in mice. However, oncogenicity in rats was indicated by a statistically significant increase in malignant pheochromocytomas of the adrenal glands of males, and a significant increase in endometrial stromal polyps in females. The principal non-oncogenic effects resulting from chronic exposure to ethoprop were hepatotoxicity, reduction of hematopoetic function, and inhibition of cholinesterase activity. In dogs, the LOEL for hepatotoxicity (elevated SGPT and alkaline phosphatase, centrilobular vacuolation, focal necrosis, periportal fibrosis and biliary proliferation) was 1 mg/kg-day, with a NOEL of 0.025 mg/kg-day. The NOEL for effects on the hematopoetic system (reduced red blood cell counts, decreased hemoglobin levels, and reduced hematocrit) in dogs was 1 mg/kg-day. Male mice exhibited preneoplastic hepatocellular lesions (hyperplastic nodules and foci of cellular alterations), with a NOEL of 4.9 mg/kg-day. The NOEL for inhibition of plasma, red blood cell and brain cholinesterase activity in the mouse was 0.3 mg/kg-day. The NOEL for inhibition of brain ChE activity in rats was 0.05 mg/kg-day.

Dietary - Rat

Crl:CD(SD)BR VAF/Plus rats (80 or 90/sex/dose) were fed ethoprop (95.6% purity) at 0, 1, 60, or 400 ppm (reduced from 600 ppm in week 3) in the diet for 104 weeks (Williams, 1992). The approximate dosages, calculated from food consumption data, were 0, 0.03, 2.1 and 16.2 mg/kg-day for males; and 0, 0.05, 2.8 and 21.3 mg/kg-day for females. At 400 ppm, females exhibited tremors and a significantly ($P<0.05$) decreased body weight (7-20%). Males exhibited significantly ($P<0.05$) decreased relative weights in the kidneys (21%) and right adrenal glands (44%). Relative organ weights of females did not decline. Statistical analysis indicated a significant ($P<0.05$) trend in C-cell carcinomas in the thyroid of males associated with dose (Table 3). However, the incidence (3/86) at the highest dose (400 ppm) was not significantly different from controls (0/86). Benign pheochromocytomas of the adrenal glands of males were first reported at 88 weeks, and malignant pheochromocytomas at 103 weeks. The incidence of malignant pheochromocytomas in males at the high dose (400 ppm) was significantly ($P<0.05$) greater than that of concomitant controls, and the trend analysis was positive. Females at 400 ppm exhibited a significantly ($P<0.05$) greater number of endometrial stromal polyps compared to controls, and the trend analysis was positive. However, the endometrial stromal polyps were not considered neoplasms by the study pathologist as there was "no cell atypia or aggressive behavior of the tissue". The NOEL for endometrial stromal polyps was 60 ppm (approximately 2.8 mg/kg-day). Throughout the study, plasma cholinesterase activity was significantly ($P<0.05$) inhibited at 60 and 400 ppm in both males and females (mean values over the two year period were 63-61% and 77-76%, respectively). Red blood cell cholinesterase activity was significantly ($P<0.05$) inhibited at 60 and 400 ppm in both males or females (mean values over the two year period were 34-39% and 41-41%, respectively). Brain cholinesterase activity in both males and females was significantly ($P<0.05$) inhibited at 60 and 400 ppm (mean values over the two year period were 33-32% and 64-66%, respectively). The NOEL for inhibition of brain cholinesterase was 1 ppm (approximately 0.05 mg/kg-day). The study was acceptable to DPR under the provisions of FIFRA.

Table 3 - Incidence of histopathological changes in rats due to dietary exposure to ethoprop (Williams, 1992).

	Male				Female			
	Dosage (mg/kg-day)				Dosage (mg/kg-day)			
Tissue	0	0.03	2.1	16.2	0	0.05	2.8	21.3
Thyroid								
C-cell adenoma[a]	9/86 (10%)	6/75 (8%)	9/76 (12%)	14/86 (16%)	10/87 (11%)	8/73 (11%)	11/78 (14%)	12/86 (14%)
C-cell carcinoma	0/86+ (0)	0/75	1/76 (1%)	3/86 (3%)	1/87 (1%)	1/73 (1%)	1/78 (1%)	2/86 (2%)
Combined	9/86 (10%)	6/75 (8%)	10/76 (13%)	17/86 (20%)	11/87 (12%)	9/73 (12%)	12/78 (15%)	14/86 (16%)
Uterus								
Endometrial stromal polyp	-	-	-	-	1/87++ (1%)	2/54 (4%)	3/45 (7%)	7/86* (8%)
Adrenal								
Pheochromocytoma[b]								
Benign	14/48 (29%)	7/48 (16%)	7/49 (15%)	5/60 (6%)	3/44 (6%)	2/45 (4%)	1/53 (2%)	2/57 (4%)
Malignant	0/48+ (0)	2/48 (4%)	2/49 (4%)	5/60* (8%)	0/44 (0)	0/45 (0)	0/53 (0)	0/57 (0)
Combined	14/48 (29%)	9/48 (20%)	9/49 (19%)	10/60 (17%)	3/44 (6%)	2/45 (4%)	1/53 (2%)	2/57 (4%)

a/ Animals at risk were those living longer than 57 weeks [the first appearance of C-cell adenomas; C-cell carcinomas were first reported at 71 weeks].
b/ Animals at risk were those living longer than 88 weeks [the first appearance of benign pheochromocytomas; malignant pheochromocytomas appeared at 103 weeks].
* Significantly (P<0.05) different from control by Fisher's exact test.
\+ Statistically significant (P<0.05) by Peto's trend test
++ Statistically significant (P<0.01) by Peto's trend test

In a modified combined study of chronic toxicity and oncogenicity, Fisher 344 rats (10 males/dose and 20 females/dose) were exposed to technical ethoprop (95.3% purity) in the diet at 0, 60.5, 131, or 262 ppm for 8 weeks prior to mating through weaning of F_1 pups (Barnett, 1983). The F_1 pups (60/sex/dose) received ethoprop in the diet at 0, 4.5, 9, or 18 ppm for weeks 0-12 and at 0, 49, 98, or 196 ppm for weeks 13-109. Ten rats from the F_1 generation/sex/dose were necropsied at 52 weeks, and the remaining rats were necropsied at 109 weeks. Observed dose-related decreases in food consumption, body weight, and survival of F_1 rats may be due to prenatal, neonatal, and/or adult exposures. There was a statistically significant (P<0.05) increase in the incidence of thyroid C-cell adenomas in males (10/46) at 196 ppm (approximately 6.2 mg/kg-day from consumption data) compared to controls (3/47). A significant trend (P<0.01, Peto's trend test) was also indicated (an incidence of 3/47; 4/43; 0/44;

10/46 for the four respective groups). In females, there was a statistically significant ($P<0.01$) trend in uterine endometrial polyps at 0, 48, 98, and 198 ppm (0/44; 4/46; 8/39; 13/44 respectively). Plasma cholinesterase activity was significantly ($P<0.01$) inhibited at 49, 98 and 196 ppm in both males (81%, 84%, and 86%, respectively) and females (89%, 91% and 93%, respectively). Red blood cell cholinesterase activity was not significantly inhibited at any dose in either males or females. Brain cholinesterase activity in males was significantly ($P<0.01$) inhibited at 98 and 196 ppm (45% and 78%, respectively). In females, brain cholinesterase activity was significantly inhibited at 49, 98 and 196 ppm (30%, 50%, and 65%, respectively). There was no NOEL for inhibition of brain cholinesterase activity. The study was unacceptable to DPR under the provisions of FIFRA due to a change in dose levels at 3 months, the lack of clinical chemistries at 6 or 18 months, and the lack of ophthalmoscopic examinations. The data do add to the weight of evidence that ethoprop induces an increased incidence of thyroid C-cell tumors and endometrial polyps.

Technical ethoprop (94-96% purity) was administered to Fischer 344 rats (70/sex/group) at 0, 1.0, 10, or 100 ppm (approximately 0, 0.05, 0.5 or 5.3 mg/kg-day for males and 0, 0.06, 0.6 or 6.6 mg/kg-day for females from consumption data) for 24 months (Spicer, 1985). Ten rats/sex/group were necropsied at 12 and 18 months. Plasma ChE activity was reduced significantly in both males and females at 10 ppm and at 100 ppm at all intervals (Table 4). Red blood cell ChE activity was significantly inhibited in both males and females at 10 ppm and 100 ppm at all intervals. Brain ChE activity was inhibited in both males and females only at 100 ppm. The NOEL for inhibition of red blood cell and serum ChE activity was 0.05 mg/kg-day in males. The NOEL for inhibition of brain cholinesterase activity was 0.5 mg/kg-day in males. No other effects, clinical signs, or pathological lesions related to the ethoprop treatment were observed. The study was considered unacceptable to DPR under FIFRA as the maximum tolerated dose (MTD) was not reached.

Table 4. Inhibition of cholinesterase activity in Fischer rats dosed with ethoprop in the diet for up to 2 years (Spicer, 1985).

	Male Dosage (mg/kg-day)			Female Dosage (mg/kg-day)		
Tissue/Time	0.05	0.5	5.3	0.06	0.6	6.6
Plasma ChE[a]						
6 mo	7%	29%**	71%**	6%	59%**	94%**
12 mo	6%	35%**	76%**	0	54%**	93%**
18 mo	0%	45%**	80%**	8%	63%**	94%**
24 mo	0%	60%**	87%**	0	63%**	94%**
RBC ChE[a]						
6 mo	0	10%*	43%**	0	19%**	42%**
12 mo	0	13%*	45%**	4%	21%**	44%**
18 mo	0	5%	37%**	4%	27%**	44%**
24 mo	2%	14%**	35%**	0	4%	28%**
Brain ChE[a]						
12 mo	0	0	28%**	0	5%	48%**
18 mo	0	0	27%**	0	0	44%**
24 mo	6%	9%	35%**	0	0	36%**

a/ N = 10.
* Significantly different (P<0.05) from control group mean by Dunnett's test.
** Significantly different (P<0.01) from control group mean by Dunnett's test.

Capsule - Dog

Technical ethoprop (96.1% purity) was administered in peanut oil at 0, 0.025, 1, or 10 mg/kg-day by capsule orally to beagle dogs (4/sex/dose) for 1 year (Brown, 1986). Plasma and RBC ChE activities were inhibited in males and females at all dose levels and intervals (6, 13, 26, and 52 weeks), but inhibition (mean values ranging from 70-85% during the year for both sexes) was only statistically significant ($p \leq 0.05$) at the highest dosage (10 mg/kg-day). Brain ChE activity was significantly ($p \leq 0.05$) inhibited (44%) at the high dosage in males. No cholinergic signs were observed. The NOEL for inhibition of brain cholinesterase activity was 1 mg/kg-day. Hepatotoxicity, indicated by elevated mean serum glutamate pyruvate transaminase, centrilobular vacuolation, focal necrosis, periportal fibrosis and biliary proliferation, was observed at 10 mg/kg-day (Table 5). One of the dogs dosed at 10 mg/kg-day was moribund. In the moribund dog, the features of anterior peritonitis and hemorrhage were considered by the pathologist to be secondary to the hepatopathy. Animals in the 1 mg/kg-day group also had centrilobular vacuolation in the liver. The NOEL for hepatotoxicity was 0.025 mg/kg-day. Significantly (P<0.01) reduced red blood cell counts, hemoglobin levels, and hematocrit were noted at 10 mg/kg-day (mean values were 15-16%, 19%, 14-17%, respectively) in males at 6, 13, 26 and 52 weeks. In females dosed with 10 mg/kg-day, significantly (P<0.05) reduced red blood cell counts (mean values were 9-14%) at 13 and 26 weeks, reduced (P<0.05) hemoglobin levels (9%) at 13 weeks, and reduced (P<0.05) hematocrit (6%) at 6 weeks were noted. The NOEL for a statistically significant reduction of blood parameters, indicative of hematopoetic toxicity was 1 mg/kg-day. The study was acceptable to DPR under FIFRA requirements.

Table 5. Changes in blood chemistry and hepatic histopathology in dogs dosed with ethoprop in capsular form for 1 year (Brown, 1986).

	Male				Female			
	Dosage (mg/kg-day)				Dosage (mg/kg-day)			
Parameter/time	0	0.025	1.0	10	0	0.025	1.0	10
Cholecystitis	0/4	0/4	0/4	2/4	0/4	0/4	0/4	4/4
Billiary prolif.	0/4	0/4	0/4	4/4	0/4	0/4	0/4	4/4
Centrilobular Vac.	0/4	0/4	3/4	4/4	0/4	0/4	3/4	4/4
Focal necrosis	0/4	0/4	0/4	2/4	1/4	0/4	0/4	1/4
Periportal fibrosis	0/4	0/4	0/4	4/4	0/4	0/4	0/4	4/4
Kupffer cell pigment	0/4	0/4	1/4	4/4	0/4	0/4	1/4	4/4
Serum GPT[a]								
6 weeks	39±4	46±10	50±8	66±19*	42±13	29±5	38±5	50±16
13 weeks	48±9	48±11	66±13	84±33	37±8	32±10	43±6	46±11
26 weeks	55±13	59±15	72±15	86±35	34±11	29±7	42±6	57±38
52 weeks	51±5	46±6	56±11	179±227	30±4	27±7	35±7	43±21
Serum Alkaline Phos.[a]								
6 weeks	210±13	234±26	239±67	260±54	274±67	200±41	247±36	300±50
13 weeks	169±24	191±30	191±56	232±54	224±48	170±34	198±35	239±62
26 weeks	100±24	114±20	131±57	166±53	176±51	107±39	128±33	135±60
52 weeks	95±17	89±20	101±52	590±905	141±41	127±70	103±26	117±50

a/ Mean ± s.d. of IU/ml from four dogs.
* Significantly different (P<0.05) from control value by Dunnett's test.

Dietary - Mouse

Technical ethoprop was administered in the diet of B6C3F1 mice (50/sex/group) at 0, 15, 30, and 60 ppm (approximately 0, 2.5, 4.9, and 9.8 mg/kg-day for males and 2.7, 5.3, and 10.8 mg/kg-day for females; from consumption data) for 18 months (Davidson and Voss, 1983). Excessive mortality occurred in weeks 55 and 56 due to a ten-fold dosing error in week 54. Ocular effects were noted, but a dose relationship could not be established due to the dosing error. At the end of the study, plasma and RBC ChE activities were significantly reduced (≤0.05) at all doses (mean values ranging from 62% at the low dose to 84% at the high dose for RBC ChE and 30-72% for plasma ChE). No clear evidence for oncogenic effects was reported. There was a positive trend for preneoplastic hepatocellular lesions (hyperplastic nodules and foci of cellular alterations), first reported at 55 weeks of age. The combined incidences of preneoplastic hepatocellular lesions for all animals at risk (55 weeks or older) at 0, 15, 30 and 60 ppm were 1/51, 1/55, 3/56, and 8/54, respectively. The study was compromised by uncontrolled factors, dosing errors, and lack of a maximum tolerated dose. The study was unacceptable to DPR under the FIFRA Guideline requirements.

In a combined chronic toxicity and oncogenicity study, ethoprop (94.6% purity) was fed to B6C3F1 mice (80/sex/dose) at 0, 0.2, 2, or 30 ppm (approximately 0, 0.03, 0.3, and 4.7 mg/kg-day for males; 0.04, 0.4 and 5.9 mg/kg-day for females; from consumption data) for 104 weeks (Inoue, 1984). Mice (10/sex/dose) were necropsied at 26, 52, and 78 weeks. Ethoprop was not oncogenic in this study, as the incidence of neoplastic lesions in treated animals was not significantly different from controls. In males, at 78 weeks the mean percent inhibition of plasma, red blood cell, and brain cholinesterase activity at 30 ppm was 77%, 81%, and 36%, respectively. However, no clinical signs were associated with this inhibition. The NOEL for ChE activity inhibition in red blood cells and brain of males was 0.3 mg/kg-day. Plasma ChE

activity was significantly (P<0.05) inhibited (20%) in females at 0.4 mg/kg-day. Consequently, the NOEL for inhibition of plasma cholinesterase activity was 0.04 mg/kg-day. The study was acceptable to DPR as an oncogenicity study, but unacceptable as a chronic toxicity study under FIFRA guidelines as there were no ophthalmologic examinations.

E. GENOTOXICITY

Summary. Ethoprop was not mutagenic in *in vitro* eucaryotic and microbial tests. Ethoprop did not induce unscheduled DNA synthesis in rat hepatocytes and did not increase the mutation frequency in mouse lymphoma and Chinese hamster ovary cells. No chromosomal aberrations were observed in the bone marrow cells of rats treated with ethoprop. However, positive effects were observed in the SCE assay and a chromosomal aberration test using Chinese hamster ovary cells *in vitro*. A dominant lethal assay conducted in rats also showed positive results. Ethoprop is considered to have genotoxic potential.

Gene Mutation

Ethoprop (specific gravity 1.094; purity not stated) was tested with *Salmonella* strains TA1535, TA1537, TA1538, TA98 and TA100, with and without rat liver S9 activation, at 0, 10, 33, 100, 333, or 1,000 *u*g/plate in triplicate, single trial (Barfknecht, 1985a). A cytotoxicity test at 1666 and 5000 *u*g/plate showed inhibition of growth. There was no increase in reversion rate with or without metabolic activation. The study was considered acceptable to DPR. The acceptability of the genotoxicity studies is based on the Toxic Substances Control Act guidelines (Federal Register, 1985).

Technical ethoprop (specific gravity 1.094; purity not stated) was tested at 0.0316, 0.042, 0.056, 0.075, 0.100, 0.133, 0.180, and 0.237 *u*l/ml without activation, and at 0.0032, 0.0042, 0.0056, 0.0075, 0.0099, 0.0133, 0.0177, 0.0237, and 0.0316 *u*l/ml with rat liver S9 activation using mouse lymphoma (L5178Y) cells (Thompson and Blackburn, 1981). No increase in mutation frequency was reported. The study was considered acceptable to DPR.

Chinese hamster ovary cells (CHO-K1-BH4) were exposed to ethoprop (purity not stated) for 5 hours at 0, 50, 100, 150, 200, 250, 300, 350, 400 and 500 *u*g/ml without activation and at 0, 5, 10, 25, 50, 75, 100, 125 and 150 *u*g/ml with rat liver S9 activation (Stankowski, 1985). There was no evidence for an increase in forward mutation frequency. The study was considered acceptable to DPR.

Ethoprop (97.5% purity) was tested at 0.001, 0.01, 0.1, 1.0, and 5.0 *u*l/plate with or without activation on *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and *Saccharomyces cerevisiae* strain D4 (Brusick, 1976). The reversion rate was not increased. The study was unacceptable to DPR because only single plates were used and there was no evidence of cytotoxicity.

Structural Chromosomal Aberrations

A dominant lethal test on ethoprop was conducted in Sprague-Dawley rats (Putman, 1981). Technical ethoprop (specific gravity 1.094; purity not stated) was administered to 10 males per group by oral gavage at 2, 9, and 20 mg/kg for 5 consecutive days. A triethylene melamine positive control group was run concomitantly. A NOEL was not established because pre-implantation losses (week 3) and death of implants (weeks 1-6) were seen at all levels, especially at 20 mg/kg. The study was considered acceptable to DPR.

In another dominant lethal test, ethoprop (95% purity) was administered at 0, 1, 5, or 20 mg/kg by oral gavage for 5 days to 24 male CD rats per dose (Dearlove, 1987). Parental NOEL was 5 mg/kg based on the weight loss, clinical signs (tremors, urogenital staining), and death. No dominant lethal effect was observed. The study was considered acceptable to DPR.

An *in vitro* chromosome aberration analysis was conducted in Chinese hamster ovary cells treated with ethoprop (specific gravity 1.094; purity not stated) for 5 hours. This was followed by 14-18 hours of incubation without activation at 0, 50, 150 or 300 *u*g/ml, or with rat liver S9 activation at 0, 10, 30 or 60 ug/ml in trial 1 and at 0, 50, 55, 60, 65 or 70 *u*g/ml in trial 2 (SanSebastian, 1985). A positive clastogenic effect was observed at 60 *u*g/ml with activation in trial 1, and at all concentrations in trial 2 with activation indicating a possible adverse effect. The study was considered acceptable to DPR.

Other Genotoxic Effects

Ethoprop was tested in two unscheduled DNA synthesis assays using Fischer 344 rat hepatocytes. In the first study, rat hepatocytes were incubated with ethoprop (specific gravity 1.094; purity not stated) at 2.5, 5.0, 10.0, 25.0, 50.0, and 100 *u*g/ml (Myhr, 1980). No unscheduled DNA synthesis was reported. The study was considered acceptable to DPR.

In another study, rat hepatocytes were treated with ethoprop (specific gravity 1.094; purity not stated) at 0, 0.33, 1.0, 3.3, 10, 33, 100, 333, 1000, 3333 and 10,000 *u*g/well with 2 ml of medium for 18-20 hours (Barfknecht, 1985b). No evidence of an increase in unscheduled DNA synthesis was reported at doses up to 100 *u*g/well. Ethoprop was cytotoxic at doses of 333 *u*g/well, or greater. The study was considered acceptable to DPR.

An *in vitro* sister chromatid exchange (SCE) assay was conducted in Chinese hamster ovary cells. Ethoprop (specific gravity 1.094; purity not stated) was tested without metabolic activation at 0, 5, 50, 100, 200 and 350 *u*g/ml and with rat liver S9 activation, trial 1, at 0, 5, 15, 30, 50, 55 and 60 *u*g/ml and at 0, 50, 60, 65, 70 and 75 *u*g/ml in trial 2 for 5 hours treatment followed by 29 additional hours of incubation (SanSebastian, 1986). The percent of cells in the first, second, and third mitoses was scored for SCEs. No increase in SCEs was noted without activation. Regression analysis indicated statistically significant dose-dependent increases in SCEs in both trials with activation. However, the total increase did not exceed two-fold at any dose. The study was acceptable to DPR.

A metaphase analysis was conducted in bone marrow cells from Sprague-Dawley rats administered ethoprop (95.7% purity) at 2.0, 9.0, or 20.0 mg/kg by oral gavage (Skinner and Schreiner, 1981). No induction of chromosomal aberrations were observed. The study was not acceptable to DPR as no females were used, and there was no evidence of toxicity at the highest dosage.

F. REPRODUCTIVE TOXICITY

Summary. Ethoprop was not associated with specific reproductive effects in the rat. It did cause decreased mean birth weights of pups (F_{1a}, F_{1b}), a decrement in weight gain (F_{1a}, F_{1b}, F_2), and decreased weanling survival (F_{1a}) in rats. The LOEL for these effects was 7.1 mg/kg-day, with a NOEL of 1.7 mg/kg-day. The NOEL for inhibition of brain cholinesterase activity was 0.09 mg/kg-day.

Dietary - Rat

Technical ethoprop (95.3% purity) was administered in the diet to Fisher 344 rats (10 males and 20 females/group) at 0, 60.5, 131, or 262 ppm (Gulf South Research Institute, 1980). Each male was mated with 2 females. Two litters/generation were studied for 3 generations. Possible adverse effects included decreased fertility, mean litter size, and 21-day litter weights at 262 ppm. A decreased pup viability at 21-day was observed at 262 and 131 ppm. The NOEL for pup survival was 60.5 ppm. The study was unacceptable to DPR under FIFRA guidelines due to an intercurrent disease (enzootic pneumonia).

Ethoprop (95.3% purity) was administered in the diet at 0, 1, 30, or 300 ppm to CD Sprague-Dawley rats (28 rats/sex/group) through two generations (F_0, F_{1b}) with two litters in the first generation (F_{1a}, F_{1b}) and one litter in the second, F_2 (Neeper-Bradley, 1991). Approximately one week after weaning of the F_{1a} litter (week 19) the high dose was reduced to 150 ppm. Adult F_0's were continuously exposed for 10 weeks, then, through two cycles (F_{1a}, F_{1b}) of mating, gestation and lactation. Selected F_{1b} weanlings were continuously exposed for 12 to 15 weeks, then, through one cycle (F_2) of mating, gestation and lactation. The F_{1a}, F_{1b}, and F_2 litters were possibly exposed *in utero* and via mothers' milk. Body weight gains were significantly ($P<0.05$) reduced (20-49%) in F_0 adult males (weeks 0-20) and for females (7-13%) during gestation and lactation (weeks 11- 18) at the high dose level. Terminal plasma and brain cholinesterase activities were significantly ($P<0.01$) lower at 300 ppm level in F_0 males (88% and 42% inhibition, respectively) and females (97% and 47% inhibition, respectively). Significant ($P<0.05$) inhibition of plasma and brain cholinesterase activities (90% and 19%, respectively) was also observed in F_0 females at 30 ppm compared to controls. Terminal brain cholinesterase activities were significantly ($P<0.05$) lower in F_1 males (37% and 10% inhibition) and females (42% and 13% inhibition) at 150 ppm and 30 ppm, respectively. The NOEL for inhibition of brain cholinesterase activity was 1 ppm (approximately 0.09 mg/kg-day from consumption data). There were no significant treatment related effects on fertility and fecundity indexes. A possible adverse reproductive effect was indicated by significantly ($P<0.05$) decreased pup mean weight gain (F_{1a}, 29%; F_{1b}, 18%; F_2 , 9%) at 300/150 ppm and decreased weanling survival (3%) at 300 ppm (F_{1a}). The decreased weight gain for the F_{1b} pups at 300/150 ppm persisted through adulthood. The LOEL for these effects was 150 ppm (approximately 7.1 mg/kg-day from consumption data), with a NOEL of 30 ppm (approximately 1.7 mg/kg-day). This study was acceptable to DPR under FIFRA guidelines.

G. DEVELOPMENTAL TOXICITY

Summary. Ethoprop was not teratogenic in rats or rabbits. The main effects noted in developmental toxicity studies were associated with inhibition of cholinesterase activity. In rats, the LOEL for maternal toxicity (clinical signs) was 18 mg/kg-day with a 2-day NOEL of 9 mg/kg-day. The LOEL for maternal toxicity (reduced body weight gain and death) in an earlier rat study was 16 mg/kg-day with a NOEL of 1.6 mg/kg-day. In rabbits, the LOEL for maternal toxicity (cholinergic signs and death) was 5.0 mg/kg-day with a 2-day NOEL of 2.0 mg/kg-day. In a different rabbit study, the NOEL for decrement in maternal weight gain (14%) was 0.125 mg/kg-day (LOEL = 0.5 mg/kg-day).

Gavage - Rat

Technical ethoprop (95.6% purity) was administered by gavage at dosages of 0 (corn oil), 2, 9, or 18 mg/kg-day to mated Sprague-Dawley rats (25/group) on gestation days 6 through 15 (Rodwell, 1989a). A significant reduction ($p \leq 0.01$) in maternal body weight gain (100% reduction on days 6-9, and 27% reduction on days 6-16) was observed in animals at 18 mg/kg-day. Treatment related soft stools (8/25) and anogenital staining (3/25) were reported in the 18 mg/kg-day group after two days of dosing. There was no evidence of fetal effects. The NOEL based on maternal toxicity (soft stools and anogenital staining) was 9 mg/kg-day. The study was acceptable to DPR under FIFRA Guideline requirements.

Ethoprop (94% purity) was administered in corn oil at 0, 0.16, 1.6, or 16 mg/kg-day by oral gavage on days 6 through 15 of gestation to Sprague-Dawley rats (25-35 mated females/dose) (Knickerbocker and Re, 1979). At 16 mg/kg-day, ethoprop significantly increased maternal mortality (21/35 were reported to have died, but no times were given) and decreased dam weight gain (8-20%) during gestation days 6-15. No developmental effects were reported. The NOEL for developmental toxicity was greater than 16 mg/kg-day. The maternal NOEL was 1.6 mg/kg-day (maternal death, decrement in maternal weight gain). The study was acceptable to DPR under FIFRA Guideline requirements.

Gavage - Rabbit

A range finding developmental toxicity study with ethoprop was conducted in rabbits (Rodwell, 1989b). Technical ethoprop (95.6% purity) in corn oil at 0, 0.1, 0.5, 2.0, 5.0 and 10.0 mg/kg-day was administered to artificially inseminated New Zealand white rabbits (8/group) during days 6 to 18 of gestation. Maternal deaths, cholinergic signs and decreased body weight gain (8% after 3 days of treatment) were observed at 5 mg/kg-day or greater. One rabbit in the 5 mg/kg-day group died on gestation day 18, and three rabbits in the 10 mg/kg-day group died on gestation days 13, 21, 29 (one on each day). Cholinergic signs were observed in the 5 mg/kg-day (soft stools- 2/8, urine and fecal staining of the fur- 2/8) and 10 mg/kg-day (emaciation- 1/8, soft stools and diarrhea- 4/8, urine and fecal staining of the fur- 3/8) groups beginning on the second day of dosing. The cholinergic signs were more severe in the 10 mg/kg-day group. Abortions were observed in the 0.1 mg/kg-day (day 21), 5 mg/kg-day (days 21 and 28), and 10 mg/kg-day (day 23) groups, and premature delivery in the 0.1 mg/kg-day (day 29) group. As the abortions and premature delivery were not dose related, they are not considered substance related. The 2-day NOEL for maternal cholinergic signs and death was 2.0 mg/kg-day. No developmental effects were observed at any dose. The data were considered supplemental.

Based on the results of the above range finding study, technical ethoprop (95.6% purity) was administered by gavage at dosage levels of 0 (corn oil), 0.625, 1.25, and 2.5 mg/kg-day to 20 artificially inseminated New Zealand White rabbits per group on gestation days 6 through 18 (Rodwell, 1989c). No effects were observed at any tested dose. The study was acceptable to DPR under FIFRA Guideline requirements. The maternal and developmental NOEL was equal to or greater than 2.5 mg/kg-day (the highest dose tested).

Wolfe and Durloo (1981) examined the embryotoxic and teratogenic effects of ethoprop in rabbits. Technical ethoprop (95.7% purity) was administered by oral gavage in corn oil at 0, 0.125, 0.5, or 2.0 mg/kg-day to 17 New Zealand white rabbits per dosage on days 6-18 of gestation. These dosages were selected on the basis of a pilot study in which 3 of 4, 2 of 5 and 2 of 4 rabbits at dosage levels of 10, 5, and 1 mg/kg-day, respectively, died before termination of the gestation period. The data did not indicate the days on which the rabbits died, or if the deaths were compound related. In the main study, a reduced weight gain was observed at 2.0 mg/kg-day (-56 g) and 0.5 mg/kg-day (-1 g) during the dosing period. Anorexia was observed in control and treated animals during and following the dosing period with a higher incidence in the treated animals. No effect was seen on the uterine parameters, nor were any malformations or developmental variations caused by the compound. The maternal NOEL in the main study was 0.125 mg/kg-day for mean decrement (14%) in the maternal weight gain after 12 days of dosing. As no developmental effects were observed, the developmental NOEL was equal to or greater than 2.0 mg/kg-day. The study was acceptable to DPR under FIFRA Guideline requirements.

H. NEUROTOXICITY

Summary- Ethoprop caused no clinical signs of delayed neurotoxicity (locomotor ataxia), and no histopathological evidence of nerve damage in hens. In rats, the single dose NOEL for cholinergic signs, reduced motor activity, and reduced scores on the functional observational battery was 5 mg/kg. The 4-week NOEL for clinical signs and decreased performance on the functional observational battery in rats was 3.0 mg/kg-day. A single dose of ethoprop produced significant reduction in brain cholinesterase activity which persisted for up to 15 days.

Oral- hen

Technical ethoprop (94.5% purity) was administered to 63 hens by oral gavage in corn oil at 6.5 mg/kg, determined to be the LD_{50} by the laboratory, with a second dose of 5.3 mg/kg given on day 21 (Roberts *et al*, 1986). There was 70% mortality in the treated group by day 4 in spite of atropine and/or 2-PAM protection. There were no clinical signs of delayed neurotoxicity (locomotor ataxia) and no evidence of nerve damage in 16 survivors examined microscopically. All hens in the LD_{50} portion of the study, orally dosed with 1, 2, 4, 8, 16 mg/kg, exhibited clinical signs (subdued appearance). There was no NOEL. The study was acceptable to DPR under FIFRA guideline requirements.

Oral- rat

Sprague-Dawley rats (17/sex/dose) were given technical ethoprop (96.2% purity) at 0, 5, 50 or 75 mg/kg (males) and 0, 5, 25, or 50 mg/kg-day(females) in a single dose by oral gavage (Weiler, 1994a). The study was originally designed with a high dose of 90 mg/kg, but 3/4 males died on day 1 at 90 mg/kg. Two males given 75 mg/kg died on day 3. Six female rats given 50 mg/kg died on day 1 or 2. Cholinergic signs (whole body tremors, tremors of the head, non-formed feces, labored respiration, yellow haircoat, pale body, clear discharge from both eyes, protruding eyes, incoordination, hypoactivity, excessive salivation, recumbent position) were noted on day 1 in males given 50 or 75 mg/kg, and on day 1 or 2 for females dosed with 50 mg/kg. Males dosed with 50 or 75 mg/kg exhibited a significant ($P<0.05$) reduction in functional and behavioral ability, and motor activity (61% and 96%, respectively) on day 1. In females, motor activity was significantly ($P<0.05$) reduced (94%) at 50 mg/kg-day, and functional and behavioral ability was reduced at doses of 50 mg/kg and 25 mg/kg. Both males and females exhibited a significant reduction in plasma and red blood cell cholinesterase activity on day 2 (Table 6). Brain cholinesterase activity was not measured until day 15, at which point there was no significant reduction in activity at any dose. The single dose NOEL for cholinergic signs, reduced motor activity, and reduced scores on the functional observational battery was 5 mg/kg. The data were considered acceptable to DPR under FIFRA guidelines.

Table 6. Neurotoxic effects of ethoprop in Sprague-Dawley rats on day two from exposure to a single dose of ethoprop by gavage (Weiler, 1994)

	Dosage (mg/kg)			
Parameter	0	5	50	75
Males				
Plasma Cholinesterase Activity[a]	-	55%*	13%*	6%*
RBC Cholinesterase Activity[a]	-	92%	55%	45%
Females				
Plasma Cholinesterase Activity[a]	-	51%*	27%*	6%*
RBC Cholinesterase Activity[a]	-	67%	51%*	65%*

a/ Mean activity expressed as percent of control value.
* Significantly different ($P<0.05$) from control by Dunnett's test.

Technical ethoprop (95.7% purity) was administered by oral gavage to Crl:CD(SD)BR VAF/Plus rats (24/sex/group) in a single dose at 0, 30, or 60 mg/kg for males or 0, 20, 40 mg/kg for females (Weiler, 1994b). Males dosed with 60 mg/kg exhibited tremors (6/24), hunched posture (4/24), labored breathing (2/24), anogenital staining (4/24), and excessive salivation (2/24). The single dose NOEL for clinical signs was 30 mg/kg. At 30 and 60 mg/kg there was significant ($P<0.05$) inhibition of plasma cholinesterase activity (85% and 93%, respectively), red blood cell cholinesterase activity (43% and 53%, respectively), and brain cholinesterase activity in males on day 1 (Table 7). At 20 and 40 mg/kg there was significant ($P<0.05$) inhibition of plasma cholinesterase activity (85% and 93%, respectively), red blood cell cholinesterase activity (43% and 53%, respectively), and brain cholinesterase activity in females on day 1. There was no NOEL for inhibition of brain cholinesterase activity. Inhibition of cholinesterase activity in some parts of the brain was still significantly ($P<0.05$) reduced in males after 15 days. The data were considered supplemental.

Table 7. Percent inhibition of brain cholinesterase activity caused by a single, oral gavage dose of ethoprop in rats (Weiler, 1994b).

	Male		Female	
	Dosage (mg/kg)		Dosage (mg/kg)	
Time/Brain location	30	60	20	40
Day 1				
Caudate/Putamen[a]	45*	93*	72*	92*
Hippocampus	45*	72*	50*	75*
Frontal Cortex	48*	76*	55*	77*
Cerebellum	46*	81*	60*	80*
Day 15				
Caudate/Putamen	9	32	25	40
Hippocampus	0	18*	4	17*
Frontal Cortex	19*	27*	32	29
Cerebellum	0	6	0	0

a/ Mean percentage inhibition; N = 6 for all measurements
* Significantly different from control (P<0.05) by Dunnett's t test.

Diet- rat

Crl:CD(SD)BR VAF/Plus rats (27/sex/group) were fed on a diet containing ethoprop (95.7% purity) at 0, 4, 40 or 400 ppm (approximately 0.26, 2.6 or 27 mg/kg-day for males; 0.31, 3.0 or 31 mg/kg-day for females from consumption data) for up to 14 weeks (Weiler, 1994c). There was a significant (P<0.05) decrement in body weight gain for males (15%) and females (6%) dosed with 400 ppm of ethoprop. After 4 weeks at 400 ppm, clinical signs [slight tremors (1F); vocalization during handling (2F); salivation and rapid/shallow respiration (1M); constant jerky movement (3M, 1F)] were observed. Mean analgesic reflex times were significantly (P<0.05) shorter for males at 400 ppm at 4 weeks. Hindlimb grip strength and motor activity was significantly (P<0.05) decreased in males at 400 ppm at 4 weeks. The 4-week NOEL for clinical signs and decreased performance on the functional observational battery was 3.0 mg/kg-day. The NOELs for inhibition of brain cholinesterase activity were 3 mg/kg-day at 4 and 8 weeks, and 0.31 mg/kg-day at 14 weeks (Table 8). The 4-week NOEL for inhibition of plasma cholinesterase activity was 0.31 mg/kg-day. Red blood cell cholinesterase activity was not affected. The study was acceptable to DPR under FIFRA guideline requirements.

Table 8. Percent inhibition of cholinesterase activity caused by ethoprop in the diet of rats for up to 14 weeks (Weiler, 1994c).

	Male			Female		
	Dosage (mg/kg-day)			Dosage (mg/kg-day)		
Time/tissue	0.26	2.6	27	0.31	3.0	31
Week 4						
Plasma ChE[a]	7	30*	26*	20	67*	97*
Caudate/Putamen	17	23*	84*	8	32	83*
Hippocampus	0	0	46*	9	18	54*
Frontal Cortex	19	0	71*	0	30	74*
Cerebellum	0	0	52*	0	13	53*
Week 8						
Plasma ChE	0	58*	85*	34*	87*	98*
Caudate/Putamen	3	11*	82*	0	0	53*
Hippocampus	0	0	59*	23	33*	67*
Frontal Cortex	10	23	61*	31	49	80*
Cerebellum	0	0	45*	0	13	53*
Week 14						
Plasma ChE	0	54*	87*	18	86*	97*
Caudate/Putamen	0	0	73*	34	49*	82*
Hippocampus	0	0	54*	23	36*	66*
Frontal Cortex	10	7	53*	52*	56*	80*
Cerebellum	9	0	49*	6	26*	59*

a/ Mean percentage inhibition; N = 9 for all measurements
* Significantly different from control (P<0.05) by Dunnett's t test.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

Ethoprop entered the risk assessment process due to its high acute toxicity, possible oncogenicity, and adverse effects on the liver caused by chronic exposure. Table 9 provides a summary of the reported toxic effects of ethoprop.

1. Acute Toxicity

The oral LD_{50} for ethoprop was 61 mg/kg in male rats, and 33 mg/kg in female rats (Powers, 1965a). Rabbits were the most sensitive laboratory species to ethoprop exposure, with a dermal LD_{50} of 24 mg/kg (Rhone-Poluenc Inc., 1986). Clinical signs of acute toxicity were characteristic of cholinesterase inhibition and included diarrhea, excessive urination, lacrimation, tremors and convulsions, and sometimes death (Dudek, 1984; Smith, 1984a,b; Powers, 1965; Myers, 1986; Nachreiner, 1986).

The principal route of exposure for most pesticide applicators using ethoprop was through the skin (Appendix A). Consequently, it is generally preferable to use the dose-response of adverse effects observed in short-term dermal toxicity studies as the basis for calculating margins of safety for workers with short-term exposure to ethoprop. The dermal LD_{50} for technical ethoprop in rabbits was 24 mg ethoprop/kg (Rhone-Poulenc Inc. 1986). However, none of the submitted or published data established a single dose dermal NOEL for clinical signs in rats or rabbits using technical ethoprop. In rats, a single dermal dose of Mocap® 6EC resulted in cholinergic signs (salivation, irregular respiration, prostration, and morbidity), with a NOEL of 160 mg formulation/kg (Morrow, 1984). Dermal exposure of rabbits to Mocap® 6EC resulted in clinical signs (ataxia, depression, dilation of pupils, excessive salivation, and loss of the righting reflex) with a NOEL of 8.7 mg ethoprop/kg (Saunders, 1972). However, examination of the database suggests that ethoprop, diluted in formulations, has more toxicity through the dermal route than technical grade ethoprop (Table 2; Knaak *et al.*, 1986). This suggests that the inert ingredients in the formulation may have facilitated the passage of ethoprop through the skin. Therefore, none of the short-term dermal toxicity studies were appropriate as the basis for calculating margins of safety for short-term occupational exposures.

Instead of a dermal NOEL, the absorbed dose from an oral NOEL was used to estimate margins of safety from short-term exposure to ethoprop. Short-term oral NOELs were derived from developmental studies in rats and rabbits, and from a single dose neurotoxicity study in rats. Ethoprop did not produce developmental malformations in rats. Fetal toxicity in rat studies was manifested as decreased fetal weight. In rats, the LOEL for maternal toxicity (cholinergic signs- soft stools [8/25 animals] and anogenital staining [3/25 animals]) was 18 mg/kg-day with a NOEL of 9 mg/kg-day (Rodwell, 1989a). The effects were manifested after two days of dosing. A lower NOEL for cholinergic signs (1.6 mg/kg-day) was reported in an earlier rat developmental study (Knickerbocker and Re, 1979). However, the happenstance of dose selection appeared to determine this NOEL. As the LOEL in the earlier study (Knickerbocker and Re, 1979) was 16 mg/kg-day, the NOEL (9 mg/kg-day) from the later study (Rodwell, 1989a) was not precluded as a possible NOEL for the earlier study as well. The single dose LOEL for cholinergic signs, reduced motor activity, and reduced scores on the functional observational battery was 25 mg/kg with a NOEL of 5 mg/kg in both male and female rats. Again, 9 mg/kg is not precluded as the actual NOEL.

Developmental toxicity was not observed in rabbits at any dose. Maternal toxicity in rabbits, characterized by signs of cholinesterase inhibition (soft stools [2/8 animals], anogenital staining [2/8 animals], and death [1/8 animals]), was observed by day two at 5.0 mg/kg-day, with a NOEL of 2.0 mg/kg-day (Rodwell, 1989b). A lower NOEL in rabbits, 0.125 mg/kg for decrement in maternal weight gain (14%), was noted in an earlier study (Wolfe and Durloo, 1981). However, the endpoint (decrement weight gain) required 12 days of dosing and was not considered an adverse effect. Consequently, this NOEL could not be used to assess health risks associated with potential single dose exposures to ethoprop. The NOEL (2 mg/kg-day) for maternal toxicity in rabbits (cholinergic signs and death) was used to assess the health risks from potential short-term exposures to ethoprop.

2. Chronic Toxicity

The principal non-oncogenic effects resulting from chronic exposure to ethoprop were inhibition of cholinesterase activity, hepatotoxicity, and reduction of hematopoetic function. Chronic exposure to ethoprop in the diet also produced reproductive effects in rats (decreased pup mean birth weights, weight gain, and decreased weanling survival), with a NOEL of 1.5 mg/kg-day. The reproductive effects appeared to be non-specific, and secondary to the decreased weight gain observed in treated, parental rats. Inhibition of cholinesterase (RBC, plasma and brain) activity was observed in rats and mice after chronic dietary exposure to ethoprop, and in dogs after chronic capsular exposure. The 2-year NOEL for inhibition of red blood cell and brain cholinesterase activity in the mouse was 0.3 mg/kg-day (Inoue, 1984). The 2-year NOEL for inhibition of brain ChE activity in rats was 0.05 mg/kg-day (Williams, 1992). The 1-year NOEL for inhibition of brain cholinesterase activity in dogs was 1 mg/kg-day (Brown, 1986).

Male mice exhibited preneoplastic hepatocellular lesions (hyperplastic nodules and foci of cellular alterations), with a NOEL of 4.9 mg/kg-day (Inoue, 1984). Hepatotoxic effects resulting from long term exposure of dogs to ethoprop by the oral route were manifested as centrilobular vacuolation, focal necrosis, periportal fibrosis and/or biliary proliferation (Brown, 1986). The NOEL for these hepatotoxic effects in dogs was 0.025 mg/kg-day. The hematopoetic system in dogs was also compromised as red blood cell counts, hemoglobin levels, and hematocrit were all decreased in both males and females at dosages of 10 mg/kg-day or greater. The NOEL for these hematopoetic effects was 1 mg/kg-day. The NOEL for hepatotoxicity, 0.025 mg/kg-day, was used to assess margins of safety for potential chronic exposure to ethoprop.

3. Oncogenic Effects

The weight of evidence for the oncogenic potential of ethoprop is weak. Ethoprop is considered to have genotoxic potential because it induced chromosomal aberrations *in vitro* (SanSebastian, 1985), and positive results were reported in a dominant lethal test (Putman, 1981). However, ethoprop did not cause DNA damage or mutations *in vitro*. Three types of tumors were potentially associated with long-term, laboratory exposure of rats to ethoprop. **1)** In two studies, two different strains of female rats developed uterine polyps in response to dietary exposure to ethoprop (Barnett, 1983; Williams, 1992). However, the oncogenic significance of this effect is questionable as a) no other uterine effects were reported; b) the endometrial stromal polyps were not considered neoplasms by the pathologist as there was "no cell atypia or aggressive behavior of the tissue" and, c) the polyps were not associated with any specific cause of death. **2)** Ethoprop appeared to cause a dose-related increase in thyroid C-cell carcinomas in male Sprague-Dawley rats (Williams, 1992). However, the incidence at the high dosage was not significantly different from the concurrent controls. In an earlier study

(Barnett, 1983), an increased incidence of thyroid C-cell adenomas in male F344 rats was observed. However, there was no clear dose response, and the data were insufficient to permit quantitative risk assessment. **3)** Malignant pheochromocytomas of the adrenals, which have been observed historically in conjunction with proliferative lesions of thyroid C-cells (Hamlin and Banas, 1990), were also observed in male rats in response to dietary exposure to ethoprop (Williams, 1992). The incidence at the high dosage (8%) was significantly ($P<0.05$) greater than concurrent controls (0%), and there was a significant ($P<0.05$) dose response based on Peto's trend test. The incidence of benign pheochromocytomas in control animals was twice that of any treatment group. Thus, combining benign and malignant pheochromocytomas resulted in no statistically significant trend or pair-wise differences between treated and control animals. However, the possibility remains that there could be a progression from benign to malignant pheochromocytomas which resulted from ethoprop treatment.

Although the weight of evidence suggesting ethoprop has oncogenic potential was weak, a quantitative risk assessment, based on the incidence of malignant pheochromocytomas in male rats (Williams, 1992), was conducted. The potency of ethoprop for humans (slope of the estimated risk/dose curve) was calculated using the Global 86 linear multistage model (Howe *et al.*, 1986). An interspecies scaling factor, $(\text{body weight})^{3/4}$, was used to adjust for species differences. The maximum likelihood estimate of the potency (q_1) was 2.8×10^{-2}, and the 95% upper bound estimate of the potency (q_1^*) was 6.5×10^{-2} (Appendix A).

Table 9 - Summary of Selected Ethoprop Toxicity Studies

STUDY	SPECIES	ROUTE	EFFECT	LOEL (mg/kg-day)	NOEL (mg/kg-day)	GENOTOXIC	REF[a]
neurotox	rat	gavage	clinical signs	25	5		1
subchronic	rabbit	dermal	ChE (all)	0.7	0.07		2
subchronic	mouse	diet	death, clinical signs	30	15		3
subchronic	dog	capsule	Plasma ChE inhibition	0.025	0.01		4
combined	rat	diet	Brain ChE	2.1	0.05		5*
combined	rat	diet	endometrial polyps	21.3	2.8		5*
combined	rat	diet	Brain ChE inhibition	5.3	0.5		6
chronic	dog	capsule	hepatotox., hematopoetic effects	1	0.025		7*†
oncogenicity	mouse	diet	hepatocellular lesions, ChE		<2.5		8
oncogenicity	mouse	diet	RBC and Brain ChE	4.7	0.3		9
develop.	rat	gavage	soft stools, decr. in wt. gain	9	2		10*
develop.	rat	gavage	maternal death and fetal wt	16	1.6		11*
develop.	rabbit	gavage	mat. mort. and clinical signs	5	2		12†
develop.	rabbit	gavage	-		>2.5		13*
develop.	rabbit	gavage	decrement maternal weight gain	0.5	0.125		14*
repro.	rat	diet	pup weight, weanling survival	7.5	1.5		15*
gene mut.	bacteria	*in vitro*				-	16*
gene mut.	bacteria	*in vitro*				-	17
gene mut.	mouse lym.	*in vitro*				-	18*
gene mut.s	CHO cells	*in vitro*				-	19*
chromosome	bone mar.	*in vivo*				-	20
dom. lethal	rat	*in vivo*				+	21*
dom. lethal	rat	*in vivo*				-	22*
chromosome	CHO cells	*in vitro*				+	23*
Unsched DNA	rat hepat.	*in vitro*				-	24*,25*
SCE	CHO cells	*in vitro*				+	26*

References- 1. Weiler, 1994; 2. Henwood, 1989; 3. McGee, 1988; 4. Hamada, 1990; 5. Williams, 1992; 6. Spicer, 1985; 7. Brown, 1986; 8. Davidson and Voss, 1983; 9. Inoue, 1984; 10. Rodwell, 1989a; 11. Knickerbocker, 1979; 12. Rodwell, 1989b; 13. Rodwell, 1989c; 14. Wolfe and Durloo, 1981; 15. Neeper-Bradley, 1991; 16. Barfknecht, 1985a; 17. Brusick, 1976; 18. Thompson and Blackburn, 1981; 19. Stankowski, 1985; 20. Skinner and Schreiner, 1981; 21. Putman, 1981; 22. Dearlove, 1987; 23. SanSebastian, 1985; 24. Myhr, 1980; 25. Barfknecht, 1985b; 26. SanSebastian, 1986.

* Study acceptable to DPR based on FIFRA guidelines or TSCA guidelines.

† NOEL in study used as the basis for calculating margins of safety.

B. EXPOSURE ASSESSMENT

1. Occupational Exposure

Occupational exposures to ethoprop were calculated by the Worker Health and Safety Branch of DPR. They concluded that the primary route of occupational exposure to ethoprop was via the dermal route, and to a much lesser extent through inhalation (Appendix A). Exposure estimates for the various occupational categories are summarized in Table 10. These were based on monitoring data and calculations from monitoring data for surrogate active ingredients (diazinon, turbofos) with similar application rates and chemical properties. These estimates were based on 8-hr work days during the application season and assumed 100% dermal absorption. Uptake of ethoprop by the inhalation route was assumed to involve 50% retention by the lungs, and 100% absorption. The Average Daily Dosage (ADD) ranged from 0.2 *u*g/kg-day for irrigators to 139 *u*g/kg-day for incorporators (workers incorporating the applied ethoprop into the soil) working with the EC formulation. The 95th percentile of short-term exposure [geometric mean x (standard deviation)$^{1.645}$] for loader/applicator/ incorporators working with the 5G and 10G formulations were 71 *u*g/kg-day and 45 *u*g/kg-day, respectively. Mixer/loader/applicators and incorporators working with the EC formulation, and loader/applicator/incorporators working with the 10G formulation are expected to have 10 days of exposure each year. Loader/applicator/incorporators working with the 5G formulation, and irrigators working with the EC formulation are expected to experience 20 days of exposure each year. The exposure is not seasonal because ethoprop is applied as a preplant nematocide at the beginning of two to three growing seasons each year. The Annualized Average Daily Dosage (AADD) ranged from 0.01 *u*g/kg-day for irrigators, to 3.8 *u*g/kg-day for incorporators using the EC formulation. The Lifetime Average Daily Dosage ranged from 0.006 *u*g/kg-day for irrigators, to 2.2 *u*g/kg-day for incorporators using the EC formulation.

Table 10 - Estimated occupational exposures to ethoprop

Occupation	N	ADD[a] *u*g/kg-day	AADD[b] *u*g/kg-day	LADD[c] *u*g/kg-day
EC Formulation				
Mixer/Loader/Applicator	6	62	1.70	0.97
Incorporator	1	139	3.80	2.2
Irrigator	3	0.2	0.01	0.006
5G Formulation				
Load./Appl./Incorp.[d]	10	5±5[e]	0.3	0.17
10G Formulation				
Load./Appl./Incorp.[d]	11	4.7±4.2[e]	0.1	0.06

a/ Average Daily Dosage; dermal assuming 100% absorption of dermal dose (protected exposure inside protective clothing and equipment) plus inhalation (reduced 90% for respirator protection) assuming 50% uptake of lung dose, and based on a body weight of 54.8 kg.
b/ Annual Average Daily Dosage, which is the product of the daily dosage and the days exposed, divided by 365 days per year.
c/ Lifetime Average Daily Dosage; assumes 40 working years over a 70 year lifetime.
d/ Data derived from surrogate studies
e/ Geometric Mean ± S.D.

2. Dietary Exposure

Residue Data

Data for potential pesticide residues associated with USEPA and California label-approved direct food uses with tolerances, and any secondary residues in animal tissues are necessary for estimating human dietary exposures. The sources of residue data include surveillance programs conducted by the Department of Pesticide Regulation (DPR) and Federal agencies, field trials, and survey studies by registrants. Residue data obtained from the monitoring programs are preferred for human dietary assessments as they are a more realistic estimate of potential exposure. When residues are at levels higher than established tolerances, they are not utilized in the dietary exposure assessments as they are illegal. In the absence of any measured residues, the DPR dietary exposure assessments utilize surrogate data from the same crop group as defined by USEPA, or potential residues equal to USEPA tolerances (Appendix B).

The DPR has four major sampling programs: 1) priority pesticide 2) preharvest monitoring 3) produce destined for processing, and 4) marketplace surveillance. The priority pesticide program focuses on pesticides of health concern, as determined by DPR Enforcement and Medical Toxicology Branches. Samples are collected from fields known to have been treated with the specific pesticides. The preharvest monitoring program routinely examines the levels of pesticides on raw agricultural commodities in the fields at any time during the growth cycle. Generally, these data are not used unless the application schedule is known and residue data are not available from other monitoring programs. Samples of produce destined for processing are collected in the field no more than 3 days prior to harvest, or at harvest, or post-harvest before processing. For the marketplace surveillance program, samples are collected at the wholesale and retail levels, and at the point of entry for imported foods.

The U. S. Food and Drug Administration (FDA) has two monitoring programs for determining residues in food: 1) regulatory monitoring, and 2) a total diet study. The former program, like the DPR marketplace surveillance program, examines produce and processed foods at the wholesale and retail levels of trade, as well as imported produce at the point of entry. The total diet study determines residues in foods after they have been prepared for consumption.

The National Residue Program of the U. S. Department of Agriculture (USDA) provides data for potential secondary pesticide residues in meat and poultry. These residues can occur from farm animals consuming commodities or by-products in their feed.

The DPR surveillance programs from 1987-1991 indicated that ethoprop levels in RACs were non-detectable. The minimum detection limit (MDL) was 0.05 ppm. Crops monitored in this survey during 1989 and 1990 were cabbage and potatoes where ethoprop is mostly used. Field studies indicated that ethoprop residues on registered crops are less than 0.02 ppm. Examination of the FDA program for FISCAL YEAR (FY) 1985 - FISCAL YEAR (FY) 1990 revealed only two values. These were 0.680 ppm in strawberries (1987) and 0.140 ppm in apples (1989).

Tolerances are presently established at 0.02 ppm for residues of ethoprop *per se* on bananas, beans (Lima and snap), cabbage, corn, sweet corn, cucumbers, mushrooms, okra, peanuts, pineapples, potatoes, soybeans, sugarcane and sweet potatoes (Appendix B). The tolerance expired for cauliflower (April 28, 1988). There are two pending tolerances: Brussels sprouts (0.05 ppm) and grapes (0.02 ppm).

Acute Exposure

Estimates of potential acute dietary exposure used the highest measured residue values at or below the tolerance for each commodity. The following assumptions were used to estimate potential acute dietary exposure from measured residues: (1) the residue does not change over time, (2) the concentration of residue does not decrease when the raw agricultural commodity (RAC) is washed, (3) processing of RACs into various food forms does not reduce or increase the residue concentration, and (4) all foods that are consumed will contain the highest reported residue. Tolerance values for each registered commodity were used to estimate potential acute dietary exposure to ethoprop because: 1) all surveillance and field samples except two have had non-detectable levels of ethoprop residues, 2) the detection limits for the DPR organophosphate screen used for surveillance monitoring exceeds the tolerances, and 3) the tolerances are for "negligible residues", as the USEPA does not expect that any residues of ethoprop will be found on RACs (CFR, 1992a). Consequently, none of the state or federal commodity monitoring programs test for ethoprop residues.

Acute dietary exposure analyses were conducted using the Exposure-4® software program developed by Technical Assessment Systems, Inc (TAS). The Exposure-4® software program estimates the distribution of user-day (consumer-day) exposures for the overall U.S. population and specific population subgroups (TAS, 1992a). A user-day is any day in which at least one food from the specific commodity list is consumed. The consumption analysis uses individual food consumption data as reported in the 1987-88 USDA Nationwide Food Consumption Survey (USDA, 1987-88). Based on the 95% percentile of user-days exposures for all specific population subgroups, the potential acute dietary exposure of ethoprop from all labeled uses ranged from 0.13 to 0.49 *u*g/kg-day (Table 11). Non-nursing infants <1 year had the highest potential acute dietary exposure to ethoprop. The complete acute dietary exposure analysis is presented in Appendix C.

Chronic Exposure

Estimates of potential chronic dietary exposure used the average of measured and "below detection limit" residue values for each commodity. No residues were detected in the various monitoring programs. The default procedure assumed that "below detection limit" residues were equal to one-half (50%) of the tolerance for each commodity. This value was 0.01 ppm (equivalent to the lowest MDL from field studies) for each of the label approved commodities. The following assumptions were used to estimate potential chronic dietary exposures from measured residues: 1) the residue level does not change over time, 2) residues are not reduced by washing the RAC, 3) processing into various food forms does not reduce or increase the residue concentration, and 4) exposures to a commodity at all reported residue levels do occur, *i.e.* a commodity with the average calculated residue is consumed every day at an annual average level (dosage).

The potential chronic dietary exposure was calculated using the Exposure-1® software (TAS, 1992b). The food consumption data for the chronic analysis were also derived from the USDA 1987-88 Nationwide Food Consumption Survey. The foods and food-forms, and their respective residue amounts used in the analyses are presented in Appendix E. The mean potential daily dietary exposure for all population subgroups ranged from 0.02 to 0.08 *u*g/kg-day (Table 11). Children (1-6 years) had the highest potential exposure. The complete chronic dietary exposure analysis is presented in Appendix C.

Table 11. Potential acute and chronic dietary exposures to ethoprop residues

Population Subgroup	Exposure Dosage (*u*g/kg-day)	
	Acute[a]	Chronic[b]
US Pop. (all seasons)	0.22	0.04
Western Region	0.20	0.03
Nursing Infants (<1 yr)	0.42	0.03
Non-Nursing Infants (<1 yr)	0.60	0.08
Children (1-6 years)	0.42	0.09
Children (7-12 years)	0.29	0.06
Females (13+ yrs/pregnant/not nursing)	0.13	0.03
Females (13+ yrs/nursing)	0.13	0.03
Females (13-19 not preg/not nursing)	0.16	0.03
Females (20+ yrs/not preg/not nursing)	0.13	0.03
Males (13-19 years)	0.19	0.04
Males (20+ years)	0.13	0.03
Seniors (55+ years)	0.13	NA

a/ Calculated from residues equal to tolerance. Based on the upper 95th percentile for user-day exposures in all population subgroups. See Appendix C for other percentiles.
b/ Calculated using 0.01 ppm for residues below the limit of detection (0.02 ppm) for each commodity. See Appendix E for other population subgroups.
NA Not available

3. Combined Exposure

The combined exposure levels from occupational and dietary sources are listed in Tables 12 and 13 for acute and chronic conditions, respectively. Occupational exposure is the major source of exposure to ethoprop. The dietary exposure level utilized for workers was that of non-pregnant, non-nursing female adults older than 20 years of age, as this population subgroup matched the profile of the agricultural workers in Appendix A (Footnote c, Table 2).

The highest total acute exposure to ethoprop was 139 *u*g/kg-day for incorporators of the EC formulation. For irrigators associated with the EC formulation, the occupational and potential acute dietary exposures were nearly equal. Under chronic exposure conditions the combined exposures ranged from 0.04 (irrigators) to 3.83 (incorporators) *u*g/kg-day (Table 13).

Table 12 - Potential acute daily occupational, dietary, and combined exposure to ethoprop

Occupation	Occupational ADD (*u*g/kg-day)[a]	Dietary ADD (*u*g/kg-day)[b]	Combined ADD (*u*g/kg-day)
EC Formulation			
Mixer/Loader/Applicator	62	0.1	62.1
Incorporator	139	0.1	139.1
Irrigator	0.2	0.1	0.3
5G Formulation			
Load./Appl./Incorp.	5	0.1	5.1
10G Formulation			
Load./Appl./Incorp.	4.7	0.1	4.8

a/ Exposure levels taken from Table 2, Appendix A.
b/ Exposure levels for females (20+ yrs, not pregnant, not nursing) taken from Table 11.

Table 13 - Potential annual occupational, dietary, and combined exposure to ethoprop

Occupation	Occupational AADD (*u*g/kg-day)[a]	Dietary AADD (*u*g/kg-day)[b]	Combined AADD (*u*g/kg-day)
EC Formulation			
Mixer/Loader/Applicator	1.00	0.03	1.03
Incorporator	3.80	0.03	3.83
Irrigator	0.01	0.03	0.04
5G Formulation			
Load./Appl./Incorp.	0.3	0.03	0.33
10G Formulation			
Load./Appl./Incorp.	0.10	0.03	0.13

a/ Exposure levels taken from Table 2, Appendix A.
b/ Exposure levels for females (20+ yrs, not pregnant, not nursing) from Table 11.

The theoretical, combined (dietary AADD plus occupational LADD) lifetime exposures to ethoprop for each job category were mixer/loader/applicator (EC Formulation), 1.0 *u*g/kg-day; loader/applicator/incorporator (5G Formulation) 0.2 *u*g/kg-day; loader/applicator/incorporator (10G Formulation) 0.04 *u*g/kg-day; incorporator (EC Formulation) 2.2 *u*g/kg-day; and irrigator (EC Formulation) 0.04 *u*g/kg-day.

C. RISK CHARACTERIZATION

The cholinergic and hepatotoxic effects observed in animals exposed to ethoprop are considered to have a biological threshold. Exposure below a certain level is not expected to cause adverse effects. The margin of safety (MOS) for exposure to ethoprop is calculated as the ratio of an appropriate NOEL established in animal studies to the potential exposure dosage estimated for human population.

$$\text{Margin of Safety} = \frac{\text{NOEL}}{\text{Exposure Dosage}}$$

The mathematical model used to estimate the health risks from oncogenicity assumes that there is no biological threshold, and that a worker would be exposed to the same average annual level of ethoprop for 40 years. The added risk of cancer for lifetime exposure to ethoprop is the product of the MLE [2.8×10^{-2} $(\text{mg/kg-day})^{-1}$] or the 95 percent upper bound confidence limit [6.5×10^{-2} $(\text{mg/kg-day})^{-1}$] of potency for humans and the Lifetime Average Daily Dosage.

1. Occupational Exposure

The margins of safety for potential acute exposure, based on a NOEL of 2.0 mg/kg-day for cholinegic signs and death, ranged from 14 for incorporators using the EC formulation to 10,000 for the irrigators (Table 14). If the 95th percentile of short-term exposure [geometric mean x (standard deviation)$^{1.645}$] were considered for workers using the 5G and 10G formulations, the MOSs would be 29 and 40, respectively. The margins of safety for annual occupational exposure, based on a NOEL of 0.025 mg/kg-day for hepatotoxicity in dogs, ranged from 7 for incorporators using the EC formulation to 2,500 for irrigators (Table 14). The maximum likelihood estimate of added risk of cancer from lifetime exposure to ethoprop ranged from 1.7 x 10^{-7} for irrigators using the EC formulation to 6.2 x 10^{-5} for incorporators. The 95% upper confidence limit on the added risk of cancer from lifetime exposure to ethoprop ranged from 3.9 x 10^{-7} for irrigators using the EC formulation to 1.4 x 10^{-4} for incorporators.

Table 14 - Margins of safety for potential acute (daily), chronic (annual), and added risk for lifetime occupational exposures to ethoprop.

Work Task	Acute Exposure MOS[a]	Annual Exposure MOS[b]	Lifetime Exposure Added Risk[c]
EC Formulation			
Mixer/Loader/Appl.	32	15	2.7 x 10^{-5}
Incorporator	14	7	6.2 x 10^{-5}
Irrigator	10,000	2,500	1.7 x 10^{-7}
5G Formulation			
Load./Appl./Incorp.	400	83	4.8 x 10^{-6}
10G Formulation			
Load./Appl./Incorp.	426	250	1.7 x 10^{-6}

a/ Based on NOEL = 2.0 mg/kg-day for cholinegic signs and death in a rabbit study (Rodwell, 1989b). MOS = $\frac{\text{NOEL (2000 } u\text{g/kg-day)}}{\text{ADD}}$

b/ Based on a NOEL = 0.025 mg/kg-day for hepatotoxicity from a chronic dietary study in dogs (Brown, 1986). MOS = $\frac{\text{NOEL (25 } u\text{g/kg-day)}}{\text{AADD}}$

c/ The product of the MLE of potency for humans [2.8 x 10^{-2} (mg/kg-day)$^{-1}$] (Williams, 1992) and the LADD (Table 10).

2. Dietary Exposure

Acute (Daily) Exposure

The MOSs for potential acute dietary exposure to ethoprop, based on an acute NOEL of 2.0 mg/kg for cholinegic signs and death in rabbits, ranged from 3,000 for non-nursing infants (<1 year) to 15,000 for females (13+ yrs/nursing)(Table 15). Margins of safety for other population subgroups are reported in Appendix C.

Chronic (Annual) Exposure

The MOSs for annual dietary risk from the annualized daily dosage of ethoprop, based on a NOEL of 0.025 mg/kg-day for hepatotoxicity in dogs, ranged from 300 for children (1-6 years) to 1,000 for nursing infants (<1 year old) (Table 15). The MOSs for other population subgroups are reported in Appendix C.

Table 15 - Daily and annual dietary margins of safety for potential exposure to ethoprop.

Population Subgroup	Daily[a] MOS[c]	Annual[b] MOS[c]
US Pop. (all seasons)	9,000	700
Western Region	10,000	700
Nursing Infants (<1 yr)	5,000	1,000
Non-Nursing Infants (<1 yr)	3,000	300
Children (1-6 yrs)	5,000	300
Children (7-12 yrs)	7,000	400
Female (13+ yrs/pregnant/not nursing)	15,000	900
Female (13+ yrs/nursing)	15,000	900
Females (13-19 yrs/not pregnant/not nursing)	13,000	800
Female (20+ yrs/not pregnant/not nursing)	15,000	1,000
Males (13-19 yrs)	10,000	600
Male (20+ yrs)	14,000	900
Seniors (55+ yrs)	15,000	-

a/ Based on NOEL = 2.0 mg/kg-day for cholinegic signs and death in a rabbit developmental study (Rodwell, 1989b). MOS = $\frac{\text{NOEL (2000 } u\text{g/kg-day)}}{\text{ADD}}$

b/ Based on a NOEL = 0.025 mg/kg-day for hepatotoxicity from a chronic dietary study in dogs (Brown, 1986). MOS = $\frac{\text{NOEL (25 } u\text{g/kg-day)}}{\text{AADD}}$

c/ Rounded off to the nearest thousand for acute MOS, and the nearest hundred for annual MOS.

3. Combined Exposure

The MOSs and added lifetime risk of cancer for the combined exposure to ethoprop from routes associated with occupational activities, and potential acute and annual dietary exposures are shown in Table 16. The addition of a dietary component did not cause substantial changes in the MOSs or added lifetime risk of cancer that had been calculated from only occupational activities for most workers.

Table 16 - The margins of safety and added lifetime risk for potential combined occupational and dietary exposure to ethoprop

Work Task	Acute Exposure MOS[a]	Annual Exposure MOS[b]	Lifetime Exposure Added Risk[c]
EC Formulation			
Mixer/Loader/Appl.	32	15	2.8×10^{-5}
Incorporator	14	7	1.8×10^{-4}
Irrigator	6,667	833	1.1×10^{-6}
5G Formulation			
Load./Appl./Incorp.	392	76	5.6×10^{-6}
10G Formulation			
Load./Appl./Incorp.	417	227	1.1×10^{-6}

a/ Based on NOEL = 2.0 mg/kg-day for cholinergic signs and death in a rabbit developmental study (Rodwell, 1989b). MOS = $\frac{\text{NOEL (2000 } u\text{g/kg-day)}}{\text{ADD}}$

b/ Based on a NOEL = 0.025 mg/kg-day for hepatotoxicity from a chronic dietary study in dogs (Brown, 1986). MOS = $\frac{\text{NOEL (25 } u\text{g/kg-day)}}{\text{AADD}}$

c/ The product of the MLE of potency for humans [2.8×10^{-2} $(\text{mg/kg-day})^{-1}$] (Williams, 1992) and the LADD (Table 13).

V. RISK APPRAISAL

Risk assessment is a process used to evaluate the potential for exposure and the likelihood that the toxic effects of a substance may occur in humans under the specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in uncertainty in the risk characterization, which integrates all the information from the previous three processes. Qualitatively, risk assessment for all chemicals has similar types of uncertainty. However, the degree or magnitude of the uncertainty varies depending on the availability of the data and the exposure scenarios being assessed.

Risk, the probability of a compound causing an adverse health effect, is a product of the potential exposure and the toxicity of a compound. Estimation of both of these aspects involves varying degrees of uncertainty, which can affect the accuracy of the risk characterization. Overestimates of potential exposure or toxicity will lead to excessive projections of risk, while under valuation of these aspects would result in underestimates of risk. MOSs greater than 100, based on a NOEL determined in laboratory animals, would generally be considered adequate for protection against the potential toxicity of a chemical (Dourson and Stara, 1983,1985; USEPA, 1986; Davidson *et al.*, 1986). This benchmark number (MOS = 100) assumes that: a) humans are ten times more sensitive to ethoprop than the laboratory animals tested, and b) within the human population, some individuals will be ten times more sensitive to ethoprop than others. Specific areas of uncertainty associated with this risk assessment for ethoprop are delineated in the following discussion.

Acute and Chronic Toxicity

Ethoprop is a Category I pesticide, with an oral LD_{50} of 32 mg/kg in female rats, and a dermal LD_{50} of 24 mg/kg in rabbits (Powers, 1965). In both rats and rabbits the dose response curve for acute toxicity was very steep. The rabbit appeared to be the most sensitive laboratory animal to the acute toxicity of ethoprop. A single drop of technical grade ethoprop (0.1 ml) in the eye caused death in all animals tested (Weir, 1965; Munson, 1980a). Even though rabbits dosed with 2.5 mg/kg were not reported to have exhibited any clinical signs in the FIFRA guideline developmental study (Rodwell, 1989c), rabbits in the range finding study dosed with 5 mg/kg exhibited clinical signs (5/8) and death (1/8) on the second day (Rodwell, 1989b). Because of the steepness of the acute toxicity curve, the NOEL for cholinergic signs and death from the range-finding developmental toxicity study (2 mg/kg-day), rather than the NOEL for cholinergic signs (2.5 mg/kg) from the guideline study, was used as the regulatory NOEL.

The toxicological endpoint used as the basis for calculating margins of safety for potential annual exposure was hepatotoxicity in the dog. Centrilobular vacuolation, focal necrosis, periportal fibrosis, and/or biliary proliferation in the liver were observed following repetitive dosing for a year (Brown, 1986). This was consistent with liver toxicity characterized by preneoplastic hepatocellular lesions (hyperplastic nodules and foci of cellular alterations) found in mice after 18 months of dietary exposure (Inoue, 1984). However, agricultural use of ethoprop is limited to field preparation prior to planting. Consequently, workers are unlikely to encounter the type of long-term, repetitive dosing which led to hepatotoxicity in laboratory animals. If the hepatotoxic effects from intermittent exposures are reversible, then the MOSs for annual exposure to ethoprop are probably an underestimate of the actual MOSs.

Oncogenicity

The weight of evidence in support of doing a quantitative risk assessment was weak. Although ethoprop caused chromosomal aberrations *in vitro* (SanSebastian, 1985), and produced positive results in a dominant lethal test (Putman, 1981)], it was not mutagenic in either eukaryotic or microbial tests *in vitro*. Neither was there any indication of unscheduled DNA synthesis or chromosomal aberrations *in vivo*.

The *in vivo* evidence for oncogenicity was less than compelling as the principal basis for risk assessment of chronic exposure. There was no indication that ethoprop induced tumors in mice or female rats. However, the incidence of malignant pheochromocytomas in male rats (5/60) treated with the highest tested dose of ethoprop was significantly ($P<0.05$) greater than concurrent controls (0/48). Yet, the incidence of benign pheochromocytomas was greater in the controls (29%) than in the high dose rats (6%), and the combined incidence (malignant and benign) of tumors was greater in the controls (29%) than in the high dose animals (17%). It could be argued that ethoprop induced a small percentage of the benign pheochromocytomas, normally found in the control rats, to become malignant. However, it should be noted that both benign and malignant pheochromocytomas occur naturally as a function of age in rats in conjunction with proliferative lesions of thyroid C-cells (Hamlin and Banas, 1990; Williams, 1992). Further, the malignant pheochromocytomas were observed only in male laboratory rats terminated at the conclusion of the study (Williams, 1992). Thus, the malignant neoplasias were not associated with any early deaths.

Finally, there is substantial uncertainty associated with the maximum likelihood estimate of the slope for ethoprop, as Chi square analysis indicated that the data did not fit the linearized multistage model very well ($P>0.3$).

Dietary Exposure

Ethoprop is used as a pre-plant nematocide. In field studies, no detectable residues of ethoprop were found in the sampling of raw agricultural commodities (RACs). Consequently, the use of tolerance values to represent theoretical acute dietary exposure to ethoprop probably overestimates the exposure. All but two of the tolerances for ethoprop are for "negligible residues", as the USEPA does not expect that any residues of ethoprop will be found on raw agricultural commodities (Code of Federal Regulations, 1992). Similarly, the use of 50% of the tolerance values (equivalent to the MDL) to represent residue levels may also result in an overestimation of theoretical acute or annual dietary exposure as no residues were ever detected in monitoring programs.

Occupational Exposure

Acute occupational exposure data associated with applications of liquid formulations were presented as mean values. The manner in which the data were obtained and recorded did not lend itself to calculations of the variability in the numbers. Consequently, acute MOSs estimated for these work categories include approximately 50% of the workers. Acute MOSs for the remaining workers with exposure values greater than the mean would be less.

Occupational exposure data associated with applications of liquid formulations of ethoprop were derived from passive dosimetry (patch measurements for dermal exposure and ambient air concentrations) of ethoprop during the operations (Appendix A). However, the small number of individuals sampled, assumptions regarding application rates and duration of time on the job, all contribute to uncertainties in the estimation of acute or annual occupational

exposures. In particular, the estimate of exposure for incorporaters using the EC formulation was derived from data on a single individual. Because exposures for work tasks associated with applications of granular formulations of ethoprop came from surrogate data, these data carry a greater degree of uncertainty than actual measurements using ethoprop. Finally, the absence of data on the absorption of ethoprop through the dermal and inhalation routes may have also resulted in an overestimation of the occupational exposure. It was assumed that the dermal absorption of ethoprop was 100%, yet reported *in vivo* human dermal absorption for five organophosphate pesticides ranged from 8% to 46% (Wester and Maibach, 1985,1993). Dermal absorption of ethoprop by human skin *in vitro* ranged between 5 to 10-fold less than rabbit skin (Stoughton, 1986).

Combining potential occupational exposures with theoretical dietary exposures may be technically correct. However, as no ethoprop residues on raw agricultural commodities have ever been detected, dietary exposure to ethoprop is probably non-existent (see above). Consequently, any estimate of combined dietary and occupational exposure to ethoprop is probably overstated.

VI. TOLERANCE ASSESSMENT

A. BACKGROUND

A tolerance is the maximum amount of pesticide residue that may remain in or on a food, or animal feed (USEPA, 1991). The USEPA tolerance program was developed as an enforcement mechanism to identify illegal residue concentrations resulting from potential non-compliance with the product label requirements (e.g. improper application rates or methods, inadequate pre-harvest intervals, direct or indirect application to unapproved commodities). Tolerances are enforced by the FDA, USDA, and state enforcement agencies (e.g. Enforcement Branch of DPR)

The data requirements established by USEPA for tolerances include: 1) residue chemistry which includes measured residue levels from field studies, 2) environmental fate studies, 3) toxicology studies which evaluate the hazards to humans, domestic animals, and non-target organism, 4) product performance such as efficacy, and 5) product chemistry which includes physical-chemical characteristics and analytical method (Code of Federal Regulations, 1992). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications, and the proposed formulations (USEPA, 1982).

Currently, the tolerances set by the USEPA are at levels necessary for the maximum application rate and frequency, and not expected to produce deleterious health effects in humans from annual dietary exposure (USEPA, 1991). USEPA uses the Reference Dose for non-cancer risks, and negligible level (generally defined as a lifetime probability of tumor occurrence at one in a million) for cancer risks as guides to determine the appropriate levels for dietary exposure.

Assembly Bill 2161 (Bronzan and Jones, 1989) requires the DPR to "conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides". In the situation where "any pesticide use represents a dietary risk that is deleterious to the health of humans, the DPR shall prohibit or take action to modify that use or modify the tolerance....". As part of the tolerance assessment, a theoretical dietary exposure for a specific commodity and specific population subgroups can be calculated from the product of the tolerance and the daily consumption rate.

B. ACUTE EXPOSURE

An acute exposure assessment using the residue level equal to the tolerance is conducted for each individual label-approved commodity. The TAS Exposure-4® software program and the USDA National Food Consumption Survey (1987-88) are used in this assessment. The acute tolerance assessment does not routinely address multiple commodities at the tolerance levels as the probability of consuming multiple commodities at the tolerance decreases as the number of commodities included in the assessment increases. Therefore, residue levels for ethoprop were set equal to the tolerance, and the MOS, based on the upper 95th percentile for user-day exposures for each population subgroup was examined for the most highly consumed commodities (FDA, 1991). The MOSs ranged from 7,000 to 220,000 for population subgroups theoretically exposed to tolerance levels of ethoprop residues on label-approved commodities (Table 17). Only the tolerances on the most frequently consumed commodities were examined, as it is assumed that the MOSs for lesser consumed commodities would be as great or greater.

C. ANNUAL EXPOSURE

An annual exposure assessment using residues equal to the established tolerances for individual or combinations of commodities has not been conducted because it is highly improbable that an individual would chronically consume single or multiple commodities with pesticide residues at the tolerance levels. Support for this conclusion comes from FDA and DPR (formerly California Department of Food and Agriculture) pesticide monitoring programs which indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (CDFA, 1990).

Table 17 - MOS for theoretical acute dietary exposure to tolerance levels of ethoprop residues for the most highly consumed commodities[a]

Agricultural Commodity	Tolerance (ppm)	Margin of Safety (Range)[b]
Bananas	0.02	7,000 - 45,000
Cabbage	0.02	10,000 - 62,000
Corn	0.02	42,000 - 220,000
Peanuts	0.02	42,000 - 204,000
Pineapples	0.02	18,000 - 127,000
Soybeans	0.02	15,000 - 152,000
Sugarcane	0.02	53,000 - 205,000
Sweet Potatoes	0.02	8,000 - 158,000

a/ Based on the 95th percentile of user-days for all population subgroups.
b/ Rounded to the nearest thousand.

VII. CONCLUSIONS

Using the EC formulation, only irrigators had a MOS for acute exposure to ethoprop that was greater than 100, the value conventionally recommended to protect people from the toxic effects of a chemical. MOSs for mean acute exposure of loader/applicator/incorporators using either the 5G or 10G formulation were greater than 100. MOSs for the 95th percentile of short-term worker exposure for loader/applicator/incorporators using either the 5G or 10G formulation were less than 100. Under the annual exposure conditions, only EC formulation irrigators and 10G loaders/applicators/incorporators had MOSs that were greater than 100. The maximum likelihood estimate of added risk of cancer from lifetime exposure to ethoprop ranged from 1.7 x 10^{-7} for irrigators using the EC formulation to 6.2 x 10^{-5} for incorporators. The 95% upper confidence limit on the added risk of cancer from lifetime exposure to ethoprop ranged from 3.9 x 10^{-7} for irrigators using the EC formulation to 1.4 x 10^{-4} for incorporators.

Margins of safety for theoretical acute and annual dietary exposure to ethoprop by the general public were greater than 100 for all population subgroups. Tolerances for ethoprop on the most highly consumed commodities provided margins of safety ranging from 7,000 to 220,000 for theoretical acute dietary exposure in all population subgroups.

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DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Ethoprop

Chemical Code # 404, Tolerance # 262
SB-950 # 93

July 24, 1986
Revised: 1/26/87, 7/1/87, 5/9/88, 6/2/88, 3/23/89, 10/5/89, 11/20/90, 12/11/91, 5/24/93, 6/10/94, 3/8/95

I. DATA GAP STATUS

Combined (chronic & onco), rat:	No data gap, no adverse effect.
Chronic toxicity, dog:	No data gap, possible adverse effects.
Oncogenicity, mouse:	No data gap, no adverse effect.
Reproduction, rat:	No data gap, possible adverse effects.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome:	No data gap, possible adverse effects.
DNA damage:	No data gap, possible adverse effect.
Neurotoxicity:	No data gap, no adverse effect.

Toxicology one-liners are attached.

All documents through volume 108, record #'s: 134406 and 962372 were reviewed.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T950308
Revised by H. Green and S. Morris 12/11/91; M. Silva, 5/24/93, 6/10/94 & 3/8/95.

See also EPA "Guidance for the Reregistration of Pesticide Products Containing Ethoprop as the Active Ingredient," June, 1988.

These pages contain summaries only. Individual worksheets may contain additional effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

** 102, 104 118435, 127458 "104-Week Combined Chronic Toxicity and Carcinogenicity Study with Ethoprop in Rats", (Williams, K.D., Hazleton Laboratories America, Inc., Madison, WI. 53704, Report # 6224-151, 10 September 1992). Ethoprop technical (95.6% pure) was administered ad libitum in the diet for 104 weeks to Crl:CD*(SD)BR VAF/Plus* rats (80 or 90/sex/dose) at 0 (Purina Certified Rodent Chow* #5002 meal), 1, 60, and 400 ppm (reduced from 600 ppm during week 3 due to toxicity in females). Chronic NOEL = 60 ppm (Tremors in females were increased and body weights were significantly decreased (7% to 20%) at 400 ppm. Thyroid, spleen, kidney and liver weights were decreased, while testes weights were increased at 400 ppm.) No adverse effect: Oncogenicity NOEL > 400 ppm (The study was previously evaluated as having a NOEL = 60 ppm (Silva, 5/20/93), based on an apparent positive trend for endometrial stromal benign polyps in females (400 ppm) at terminal sacrifice. In addition, there was a positive trend for C cell carcinoma and malignant pheochromocytoma in males and endometrial stromal polyps in females at 400 ppm.) After evaluation of information submitted by the registrant, the tumors can be considered age-related, rather than specifically due to ethoprop. ChE NOEL = 1 ppm (reduced plasma (47% to 82% inhibition), RBC (25% to 51% inhibition), and brain (28% to 65% inhibition) ChE values at 60 and 400 ppm in both sexes.) **Acceptable**. (M. Silva, 6/3/94).

262-029 962357, "Evaluation of the Chronic Toxicity and Oncogenic Potential of Ethoprop in Fisher 344 Rats," (GSRI Project No. 413-858-41, 01/20/83; Gulf South Research Institute, New Iberia, LA, 1/20/83). Ethoprop, 95.3%; dietary exposure of F_0's to 0, 60.5, 131, or 262 ppm for 8 weeks prior to mating thru weaning of F_1 pups; dietary exposure of 60 F_1's/sex/dose to 0, 4.5, 9, or 18 ppm for weeks 0 - 12, then 0, 49, 98 or 196 for weeks 13 - 109; F_0's discarded; 10 F_1's/sex/dose necropsied at 52 weeks, remaining F_1's necropsied at 109 weeks; dose-related decreases in food consumption, body weight, and survival may be due to pre- and neo-natal exposures; MTD based on cholinesterase depression in females at 196 ppm (serum 7% and brain 35 % of control); **possible adverse effect** indicated at 196 ppm by increased incidences of thyroid C-cell adenomas in males and uterine proliferative lesions in females; study UNACCEPTABLE and not upgradeable (pre- and neo-natal exposures complicate interpretation of adult chronic effects, dose levels changed at 3 months, no 6- or 18-month clinical chemistries, no ophthalmoscopic examinations, no NOEL for cholinesterase inhibition). (Gee, 4/15/85; Morris, 02/16/88).

EPA one-liner: Supplemental, additional data required - no NOEL for cholinesterase inhibition, 6/88. The reregistration standard requested a special study in rats to determine the NOEL for cholinesterase inhibition.

262-030 thru -034; 962358 thru 962362. Addenda to 262-029; 962357. Individual data.

262-067; 058184. Addendum to 262-029; 962357. Missing pages and registrant's statements (dated 06/13/87 and 06/23/87) about CDFA's evaluation of study.

262-069 058186, "Lifetime Dietary Toxicity and Oncogenicity Study in Rats", (International Research and Development Corporation, Mattawan, MI, 04/30/85). Ethoprop, 94 - 96%; 0, 1.0, 10, or 100 ppm in the diet of 70 Fischer 344 rats/sex/dose for 24 months; 10 rats/sex/dose necropsied at 12 and 18 months; no dose-related clinical signs; NOEL = 1.0 ppm (cholinesterase inhibition - plasma and erythrocyte at 10 and 100 ppm, brain at 100 ppm); no dose-related pathological effects; **no adverse effect indicated**; study UNACCEPTABLE and not upgradeable (MTD not reached). (Morris/B Davis, 12/29/87, 02/16/88).

EPA One-liner: Core Supplementary, 1/26/89.

CONCLUSION:
The report in 102/118435 contends that the thyroid tumor incidence is higher at 400 ppm since these animals showed greater survival than controls and therefore the lesions had more time to increase in size. Thyroid changes (hyperplasia, adenoma and carcinoma), it was stated, are common age-related changes (the older the animal, the greater the occurrance). The endometrial polyps were also discounted in the report since they are considered to be benign and non-aggressive. Endometrial polyps are also considered to be age-related and therefore the increased occurrance at 400 ppm was expected. Although this information may be true, it is not possible to discount these lesions because they also were observed in an earlier study reviewed at DPR (DPR volume/record #: 262-029/962357).

Incidence of Microscopic Observations - Terminal Sacrifice

	Treatment Levels (ppm)							
	0	49	98	196	0	49	98	196
	Males				Females			
# Animals Examined	47	43	44	46	44	46	39	44
THYROID								
C-cell Adenoma	3##	4	0	10	2	7	2	4
C-cell Carcinoma	1	1	0	1	0	3	3	4
UTERUS								
Endometrial Polyps					0##	4	8	13

- Significant by trend test at $p < 0.01$ (performed by the reviewer).

In this case the survival was similar across all groups, yet there was still an increase in incidence of thyroid and uterine lesions in animals treated at 196 ppm. The effect of ethoprop on thyroid and uterus are thus considered to be treatment-related and not simply due to longer survival. M. Silva, 5/21/93.

CHRONIC TOXICITY, DOG

Subchronic Study:

262-088 086768, "A Five-Month Oral Toxicity Study with One-Month Recovery in Beagle Dogs with Ethoprop Technical", (N. N. Hamada, Hazleton Laboratories America, Inc., HLA Study No. 656-143, 4/11/90). Ethoprop technical (purity of 95.6%, lot #: 303019003) was administered by gavage in gelatin capsules at concentrations of 0 (corn oil in capsule), 0.01, 0.025, or 1.0 mg/kg/day to 6 Beagle dogs/sex/group for 20 weeks. **No adverse effect indicated.** CHE NOEL = 0.01 mg/kg/day (Plasma cholinesterase inhibition for

males = 16.7% and females = 20.4%-25.6% at 0.025 mg/kg/day and males = 73.6%-77.1% and females = 74.7%-79.6% at 1.0 mg/kg/day. Erythrocyte cholinesterase inhibition in males = 20.4%-26.4% at 1.0 mg/kg/day. Chronic NOEL > 1.0 mg/kg/day (No other treatment related observations were reported.) These data are supplemental. (Kishiyama & Silva, 10/16/90).

Chronic Study:

****262-054 048657**, "Ethoprohos 52 Week Oral (Capsule Administration) Toxicity Study in the Beagle" (HUK Project 198/16); Hazleton UK, North Yorkshire, England; 04/29/86). Ethoprop technical, 96.1%; by oral capsule in peanut oil at 10, 1, 0.025, or 0 mg/kg/day to 4 dogs/sex/dose for 1 year; **possible adverse effect** - hepatotoxicity: elevated SGPT, centrilobular vacuolation, focal necrosis, periportal fibrosis and biliary proliferation with 1 moribund at 10 mg/kg; centrilobular vacuolation only at 1 mg/kg; reduced RBC, HGB, and HCT at 10 and 1 mg/kg; NOEL = 0.025 mg/kg/day (hepatotoxicity); originally unacceptable; Martz, 01/20/87; upgraded to ACCEPTABLE by information at 262-068, 058185. (Morris/Parker, 02/22/88).

EPA: Core Supplementary. No repeat study required but a special subchronic study in dogs for a cholinesterase NOEL. 6/88 reregistration standard.

262-068 058185. Addendum to 262-054; 048657. Quantitation of dose and registrant's statements (dated 06/18/87 and 06/23/87) about CDFA's evaluation of study.

CHRONIC TOXICITY, MOUSE

262-071 062430, "Chronic Feeding and Oncogenicity Studies in Mice with Ethoprop," (Exp. # 94; Rhône-Poulenc Inc., Monmouth Junction, NJ; 12/29/84). Ethoprop, 94.6%; 0, 0.2, 2, or 30 ppm in diet of 80 mice/sex/dose for 104 weeks; 10 mice/sex/dose necropsied at 26, 52, and 78 weeks; maximum cholinesterase inhibition at 30 ppm, plasma Z 77%, erythrocyte Z 81%, brain Z 36%; no other dose-related clinical, pathological, or histological signs; no adverse effect indicated; study UNACCEPTABLE (no ophthalmologic examinations) and not upgradeable (no MTD) as a chronic toxicity study. (Morris/B. Davis, 01/12/88).

262-070 062623. Exact duplicate of 262-071 062430. Study was submitted to comply with FIFRA 6(a)(2) and contains registrant's statements (dated 09/24/87) about CDFA's evaluation of study.

262-071 062430. Also contains registrant's statements (dated 09/29/87 about CDFA's evaluation of study.

ONCOGENICITY, MOUSE

262-025-028, 962363-66, "Chronic/Oncogenic Evaluation of Ethoprop with B6C3F1 Mice", (FDRL, 1/26/83). Technical ethoprop (lot 2225-62) at 0, 15, 30, and 60 ppm in the feed for 18 months to 50/sex/group; ten-fold dosing error in week 54, causing excessive high dose mortality in weeks 55 and 56 (18 males and 9 females). Marked eye lesions (phthisis bulbi), especially in females, in all groups including controls. An extensive effort to determine the origin of this problem was unsuccessful. [Indicates diseased or defective mice, or husbandry problems (e.g. irritation from cage

detergent) -F. Martz] Because of the ophthisis bulbi, the other ocular effects are difficult of evaluate. Optic nerve gliosis and eosinophilic bodies at 30 and 60 ppm. Gliosis in females: 3/59 (control), 10/57 (15 ppm), 15/60 (30) and 22/60 (60 ppm). No clear evidence for oncogenic effects, but second review found positive trend for preneoplastic hepatocellular lesions. Initially reviewed as UNACCEPTABLE and not upgradeable: study compromised by uncontrolled/unknown factors, dosing error, and lack of an MTD, therefore insufficient information for oncogenic assessment. The six week study (see # 072723 below) justifies the dose of 60 ppm as adequate. (Gee, 4/15/85 and 3/23/89 and Martz, 6/30/87).

EPA one-liner: Supplemental based on lack of an MTD. The HDT was considered to be two times lower than the MTD. 6/88 reregistration standard.

Rebuttal located in #262-055.

262-055, No record #; Rebuttal to mouse oncogenicity study noted above (record #962363-66); narrative only with no supplemental information; no change in status. (Martz, 6/30/87).

262-078 072723, "Six Week Dietary Toxicity Study in Mice." (IRDC, 8/24/88, 347-032). Ethoprop technical, 95.9%, fed in the diet for 6 weeks at 0, 100, 200 or 400 ppm to 10/sex/group, B6C3F1 mice; purpose was to determine if 60 ppm in study #962363 was high enough; all animals died or were sacrificed at 400 ppm, 3/10 females died at 200 ppm; erythrocyte, plasma and brain cholinesterase were all inhibited at termination of survivors with brain at 37% and 28% of controls in males at 100 and 200 ppm respectively; at 41% and 32% at 100 and 200 ppm in females; food intake and body weights were lower at 200 ppm; ChE NOEL < 100 ppm (cholinesterase inhibition, clinical signs of tremor, decreased defecation). Supplementary data for dose justification for 962363-66. (Gee, 3/21/89).

**262-071 062430, "Chronic Feeding and Oncogenicity Studies in Mice with Ethoprop," (Exp. # 94; AN-PYO Center, Japan; 12/29/84). Ethoprop, 94.6%; 0, 0.2, 2, or 30 ppm in diet of 80 mice/sex/dose for 104 weeks; 10 mice/sex/dose necropsied at 26, 52, and 78 weeks; maximum cholinesterase inhibition at 30 ppm, plasma Z 77%, erythrocyte Z 81%, brain Z 36%; no other dose-related clinical, pathological, or histological signs; no adverse effect; study ACCEPTABLE as a mouse oncogenicity/carcinogenicity study only. (Morris/B. Davis, 01/12/88).

This study is not listed in the 1988 reregistration standard. (Gee, 3/22/89).

This study also contains registrant's statements (dated 09/29/87) about CDFA's evaluation of study.

262-070 062623. Exact duplicate of 262-071; 062430. Study was submitted to comply with FIFRA 6(a)(2) and contains registrant's statements (dated 09/24/87) about CDFA's evaluation of study.

262-077 067401, "Historic Control Data for B6C3F1 Mouse for the Chronic Feeding Oncogenicity Studies in Mice with Ethoprop", (Biosafety Research Center, AN-PYO Center, Japan, 12/84). Present submission contains historical control data on tumor incidences in B6C3F1 mice to supplement an original study that was submitted to comply with FIFRA 6(a)(2) (CDFA doc. #262-070, rec. # 62623; exact duplicate of 262-071; 62430). CDFA found the original study acceptable as a Oncogenicity/Carcinogenicity study only. The present submission contains no information to alter CDFA's finding of no adverse effect in the original study. (Morris/Parker, 06/02/88).

REPRODUCTION, RAT

262-023 962356, "Evaluation of Effects of Ethoprop on Reproductive Performance by a Three Generation Study in Fisher 344 Rats," (Project # 413-858-41; Gulf South Research Institute; 12/03/80). Ethoprop, 95.3%, lot # MCTR 15977; 0, 60.5, 131, or 262 ppm in diet; 10 males and 20 females/group; each male mated with 2 females; 2 litters/generation for 3 generations; all F1A, F2A, F3A, F3B weanlings, and F0, F1B, F2B adults necropsied; enzootic pneumonia; weight gain at 14 weeks of exposure of 262 ppm adults Z 10 - 20% of 0 ppm adults; **Possible adverse effects:** decreased fertility, mean litter size, and 21-day litter weights at 262 ppm, decreased 21-day pup viability at 262 and 131 ppm; NOEL = 60.5 ppm (decreased 21-day pup viability); UNACCEPTABLE and not upgradeable (intercurrent disease); Gee, 4/11/85; one-liner update. (Morris/Gee, 01/28/88).

EPA one-liner: Unacceptable - insufficient data to determine NOEL's, illness, other problems. 6/88 reregistration standard.

262-072 063205. Addendum to 262-023, 962356. Missing pages and registrant's statements (dated 09/01/87) about CDFA's evaluation of study.

****262-095 097499**, "Two-Generation Reproduction Study of Ethoprop Technical Administered in the Diet to CD* (Sprague-Dawley) Rats", T.L. Neeper-Bradley, Bushy Run Research Center, Export, PA., Laboratory Project ID 53-598, 6/6/91. Ethoprop technical (95.3% purity, lot #308187003) was tested in a reproduction study by continuous dietary exposure of 28 Sprague-Dawley rats/sex/group through 2 generations (F0, F1B) with 2 litters in the first generation (F1A, F1B) and 1 litter in the second (F2). Adult F0's were continuously exposed for 10 weeks then through two cycles (F1A, F1B) of mating, gestation, and lactation. Selected F1B weanlings were continuously exposed for 12 to 15 weeks then through one cycle (F2) of mating, gestation, and lactation. The F1A, F1B, and F2 litters were possibly exposed in utero and via mothers milk. The exposure levels were initially 0, 1, 30, or 300 ppm. Approximately one week after weaning the last F1A litter (week 19) the high dose was reduced to 150 ppm. Significant treatment-related effects on F0 adults at 300/150 ppm were decreased body weight gains for males (weeks 0 - 20) and for females during gestation and lactation (weeks 11 - 18). Terminal brain and plasma cholinesterase activities were significantly lower at 300/150 and 30 ppm in F0 and F1 adults. There was a 13% decrease in plasma cholinesterase activity in F1 adults males at 1 ppm (ChE NOEL < 1 ppm). F0 thyroid weights were reduced in males and females at 300/150 ppm. There were no significant treatment-related effects on fertility or fecundity indexes. A **possible adverse effect** was indicated by decreased pup mean birth weights (F1A, F1B) and weight gain (F1A, F1B, F2) at 300/150 ppm and decreased weanling survival at 300 ppm (F1A). The decreased weight gain for the F1B's at 300/150 ppm persisted through adulthood (reproductive NOEL = 30 ppm). The study was acceptable (H. Green and S. Morris, 12/9/91).

TERATOLOGY, RAT

**262-084 085900, "Teratology Study in Rats with Ethoprop - Final Report", (Rodwell, D.E., Springborn Life Sciences, Inc., SLS Study No. 3147.39, November 13, 1989). Technical ethoprop (purity = 95.6%, lot #: 303019003) was administered by gavage at dosage levels of 0 (corn oil), 2, 9, and 18 mg/kg/day to mated (a sperm positive vaginal smear or copulatory plug = day 0 of gestation) Sprague-Dawley rats (25/group) on gestation days 6 through 15. Maternal NOEL = 9 mg/kg/day (A significant reduction in bodyweight, bodyweight gain and food consumption was observed.) Fetal NOEL > 18 mg/kg/day (No evidence of fetal effects.) ACCEPTABLE. (Kishiyama & Silva, 10/17/90).

262-023 962355, "Teratologic Evaluation of Ethoprop MCTR-603-78 in Sprague-Dawley Rats", (Laboratory No. 5850; Food and Drug Research Laboratories, Inc.; 04/24/79, amended 06/10/85). Ethoprop, 94% pure, in corn oil; 0, 0.16, 1.6, or 16 mg/kg/day by oral gavage on days 6 - 15 of gestation to 25 - 35 mated females/dose; maternal NOEL = 1.6 mg/kg (decreased weight gain and 21/35 died at 16 mg/kg); developmental NOEL = 1.6 mg/kg (decreased fetal weight at 16 mg/kg); **no adverse effect (developmental NOEL = maternal NOEL); initially reviewed as unacceptable but upgradeable with submission of individual fetal data and dose analysis. (Gee, 04/11/85 and Gee/Parker, 07/25/86). The possible adverse effect was changed to no adverse effect by information at 262-074, 063398. (Morris/Parker, 5/9/88). Data submitted in 262-079, individual fetal data, dosing preparation and stability of ethoprop in corn oil upgrades the study to ACCEPTABLE status. (Gee, 3/22/89).

EPA one-liner: Supplemental; teratology NOEL > 16 mg/kg (HDT); maternal NOEL = 1.6 mg/kg; possible embryotoxicity at 0.16 mg/kg. Historical control data required. 6/88 reregistration standard.

262-074 063398. Addendum to 262-023 962355. The amended report contains summarized fetal information and registrant's statements (dated 09/01/87) about CDFA's evaluation of study.

262-079 067594, 067595. Addenda to 962355 upgrading study to acceptable status. Volume contains individual dam and fetal data, records of dosing preparation and stability in corn oil. (Gee, 3/22/89).

TERATOLOGY, RABBIT

Rangefinding Study:

262-089 089020 "Rangefinding Teratology Study in Rabbits with Ethoprop," (Springborn Life Sciences, Inc., Spencerville, OH, 8/24/89; Study #: 3147.40). Ethoprop technical (95.6% pure; Lot #: 303019003, SLS Test Article ID #: S89.004.3147) was used at 0 (vehicle = Mazola corn oil), 0.1, 0.5, 2.0, 5.0 and 10.0 mg/kg (adjusted for active ingredient to 100%) on artificially inseminated New Zealand white rabbits (8/group) during days 6 to 18 of gestation (day 0 = day of insemination). **No adverse effect indicated. Maternal NOEL =** 2.0 mg/kg (Maternal deaths, clinical signs and decreased bodyweight gain were observed at $\geq$ 5 mg/kg/day.) **Developmental NOEL** $\geq$ 10 mg/kg (No effects were observed at any dose.) These data are supplemental. M. Silva, 11/16/90.

Teratology Study:

**262-085 085901, "Teratology Study in Rabbits with Ethoprop - Final Report", (Rodwell, D.E., Springborn Life Sciences, Inc., SLS Study No. 3147.41, November 15, 1989). Technical ethoprop (purity = 95.6%, lot #: 303019003) administered by gavage at dosage levels of 0 (corn oil), 0.625, 1.25, and 2.5 mg/kg/day to 20 artificially inseminated New Zealand White rabbits/group on gestation days 6 through 18 (insemination = day 0 of gestation). Maternal & Developmental NOEL > 2.5 mg/kg/day (No effects observed at any dose). ACCEPTABLE (An MTD was not achieved in this study, however the doses selected were justified, based on the range-finding study--089 089020.) (Kishiyama & Silva, 11/19/90).

**262-023 962354, "Rabbit teratology study Ethoprop technical - 01238101 - Final Report," (Hazleton (VA), 8/10/81). Ethoprop technical, 95.7% pure, by oral gavage in corn oil at 2.0, 0.5, 0.125, or 0 mg/kg/day to 17 New Zealand White rabbits/level on days 6-18 with cesarean on day 29 (insemination = day 0); weight loss/reduced gain @ 2.0 and 0.5 mg/kg during dosing period; no effect on uterine parameters; no dose-related or unusual malformations or variations. No adverse effect. Maternal NOEL = 0.125 mg/kg/day; NOAEL $\geq$ 2.0 mg/kg; developmental NOEL > 2.0 mg/kg/day. Original status unacceptable (Gee, 4/11/85), upgraded to complete and ACCEPTABLE by rebuttal and supplemental information located in -055, 051591. (Martz, 6/17/87).

EPA one-liner: Unacceptable. Additional data required including historical control data. 6/88 reregistration standard.

262-055 051591. Rebuttal and supplemental information to rabbit teratology study noted above (-023 962354). Consists of protocol, dosing solution analyses results, ethoprop composition, and individual raw data photocopied from laboratory notebook; supplemental information upgrades study to complete and acceptable. (Martz, 6/17/87).

Summary: In study 962354, a slight but transitional weight loss was the only "effect" (observed at $\geq$ 0.5 mg/kg). A similar effect was not observed when the study was repeated (085901) at doses up to 2.5 mg/kg. In addition, a rangefinding study was performed and no effects were observed at $\leq$ 2.0 mg/kg (the next highest dose where effects were observed was 5.0 mg/kg). Therefore, CDFA considers the NOAEL to be > 2.5 mg/kg, and the NOEL = 2.5 mg/kg (M. Silva, 11/90).

GENE MUTATION

Microbial Systems

262-004 962370, "Mutagenicity Evaluation of MSTR-64-76 (Ethoprop Technical) Final Report," (Litton Bionetics, 10/4/76). Ethoprop (97.5%) tested at 0.001, 0.01, 0.1, 1.0, and 5.0 ul/plate +/- S9 on Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100. UNACCEPTABLE, single plates, no evidence of cytotoxicity, no increase in inversion rate. (Gee, 4/12/87).

EPA one-liner: No grade, negative effect.

262-055. Rebuttal response to above study (record #962370) by consultant toxicologists who agree with CDFA review and further state that "...we cannot defend the acceptance of this study;" no change in study status. (Martz, 6/30/87).

**262-058 058399, "Ames Salmonella/Microsome Plate Test (EPA/OECD)." (Pharmakon Research International, PH 301-RP-001-85, 8/9/85). Ethoprop, sp. gravity 1.094; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation at 0, 10, 33, 100, 333 or 1000 mg/plate, in triplicate, single trial; cytotoxicity test at 1666 and 5000 mg/plate showed inhibition of growth; report includes raw data for preparation of test solutions; no increase in reversion rate. ACCEPTABLE. (Gee, 5/5/88).

Mammalian Cells

**262-024 962367, "Murine Lymphoma; Mutagenesis Assay, Heterozygous at the Thymidine Kinase Locus for Determination of the Potential Mutagenicity of Ethoprop," (Mobil, NJ, 8/24/81). Ethoprop (technical) tested at 0.0316, 0.042, 0.056, 0.075, 0.100, 0.133, 0.180, and 0.237 ul/ml without S9, 0.0032, 0.0042, 0.0056, 0.0075, 0.0099, 0.0133, 0.0177, 0.0237, and 0.0316 ul/ml with S9 with mouse lymphoma (L5178Y) cells; No increase in mutation frequency reported. ACCEPTABLE. (Gee, 4/11/85).

**262-058 058401, "CHO/HGPRT - Mammalian Cell Forward Gene Mutation Assay." (Pharmakon Research International, PH 314-RP-001-85, 8/9/85). Ethoprop, lot 304295001 [see CDFA Record # 058399 for sp. gravity]; tested with CHO-K1-BH4 with and without rat liver activation; concentrations without activation were 0, 50, 100, 150, 200, 250, 300, 350, 400 and 500 mg/ml, 5 hours, duplicate cultures; with activation at 0, 5, 10, 25, 50, 75, 100, 125 and 150 mg/ml, 5 hours; survival determined 19 hours after treatment, 7 days expression time for TG mutants; plated five 100 mm plates for mutation frequency per initial culture, 3 additional plates for cloning efficiency; cytotoxicity at 400 mg/ml and above; no evidence for increase in forward mutation frequency with treatment. ACCEPTABLE. (Gee, 5/5/88).

CHROMOSOME

262-024 962368, "Metaphase Analysis of Rat Bone Marrow Cells Treated In Vivo with Ethoprop," (Mobil, 8/27/81). Ethoprop (95.7%) tested at 2.0, 9.0 and 20.0 mg/Kg by oral gavage in Sprague-Dawley rats in bone marrow test; 6 males/group; UNACCEPTABLE, no females were used and no evidence of toxicity at the high dose which was the LD_{10}. Dosed for five days and sacrificed 6 hours after the last dose. Not upgraded by rebuttal in -055 noted below. No adverse effect indicated. (J.Gee, 4/12/85 and 7/1/87).

262-055. Rebuttal to bone marrow study noted above (#962368); no change in study status. (Gee, 7/1/87).

262-024 962371, "Activity of T1688 in the Dominant Lethal Assay in Rodents," (Microbiological Assoc., 9/17/81). Ethoprop (technical) was tested in the dominant lethal test at 2, 9, and 20 mg/Kg by oral gavage for 5 consecutive days with Sprague-Dawley rats; 10 males/group including a TEM positive control group; NOEL not established because an effect was seen at all doses with preimplantation losses (week 3) and death of implants (weeks 1-6), especially at 20 mg/kg. Males were mated 1:2 for 7 weekly intervals. Originally reviewed as unacceptable, but was upgraded by rebuttal response in -055 to ACCEPTABLE with **possible adverse effect. (Gee, 4/12/85 and 7/1/87).

262-055. Rebuttal to dominant lethal study above (#962371); with the submission of characterization of the test material, CDFA # 51584 in 262-055 and consideration of the rebuttal, the study is upgraded with a possible adverse effect. (Gee, 7/1/87).

262-076 065941. Exact duplicate of 962371.

**262-073 062429, "Dominant Lethal Study of Ethoprop Technical Administered Orally via Gavage to Cr1:COBS*CD*(SD)BR Male Rats," (ARGUS 218-004; Argus Research Laboratories, Inc., Horsham, PA; 07/28/87). Ethoprop, 95%, in 0.5% carboxymethyl cellulose, 5 ml/kg bw; 0, 1, 5, or 20 mg/kg by oral gavage for 5 days to 24 males/dose; each male mated to 2 females/week for 8 weeks; females sacrificed on day 14 of presumed gestation; adequate positive control; parental male NOEL = 5 mg/kg (3/25 died, organophosphate syndrome, and weight loss at 20 mg/kg); no dominant lethal effect observed; no adverse effect; study ACCEPTABLE. (Morris/Parker, 04/19/88).

262-073 062429. Also contains registrant's statements (dated 07/28/87) about CDFA's evaluation of study.

Comment: A possible dominant lethal effect was indicated in a first study (CDFA doc. # 262-024, rec. # 962371) but no adverse effect was demonstrated in a second study (CDFA doc. # 262-073, rec. # 062429). Registrant has submitted comments (CDFA doc. # 262-073, rec. # 062429, registrant's statements dated 07/28/87) on CDFA's findings of an adverse effect in the first study. These statements contain neither additional data nor acceptable rationale for changing CDFA's finding of an adverse effect and no NOEL in the first study. Although interpretation of the two studies appears to conflict, an acceptable study or any sound piece of evidence that indicates a possible adverse effect cannot be ignored and therefore the study status of "possible adverse effect" stands. (Morris, 5/88).

****262-058 058403**, "In vitro Chromosome Aberrations Analysis in Chinese Hamster Ovary (CHO) Cells." (Pharmakon Research International, PH 320-RP-001-85, 10/26/85). Ethoprop, lot No. 304295001, sp. gravity = 1.094; tested with CHO cells without activation at 0, 50, 150 or 300 mg/ml, 5 hours followed by 14 - 18 hours incubation; with rat liver activation at 0, 10, 30 or 60 mg/ml in trial 1 and at 0, 50, 55, 60, 65 or 70 mg/ml in trial 2; positive for clastogenic effect at all concentrations in trial 2 with activation and at 60 mg/ml with activation in trial 1; **possible adverse effect**. ACCEPTABLE. (Gee, 5/6/88).

In the EPA 1988 reregistration standard, EPA requested an acceptable in vivo chromosome study to confirm these in vitro findings. (Gee, 3/22/89).

DNA DAMAGE

**262-024 962372, "Evaluation of Mobil #1238101 (Ethoprop Technical) in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay," (Litton Bionetics, 7/81, 2478-80). Ethoprop (95.7%) tested in UDS assay at 2.5, 5.0, 10.0, 25.0, 50.0, and 100 nl/ml on Fischer 344 rat cells; nuclear grain count determined for 50 cells/slide with 150 cells total; no mutagenic effects reported. ACCEPTABLE. (Gee, 4/12/85).

262-058 058402, "Rat Hepatocyte Primary Culture/DNA Repair Test." (Pharmakon Research International, PH 311-RP-001-85, 8/9/85). Ethoprop, lot no. 304295001, sp. gravity = 1.094; tested with primary hepatocytes from a male Fisher 344 rat at 0, 0.33, 1.0, 3.3, 10, 33, 100, 333, 1000, 3333 and 10,000 mg/well with 2 ml medium, 18 - 20 hours exposure, grain counts by autoradiography; triplicate cultures, scored 50 cells per coverslip for a total of 150 cells; net nuclear counts; no evidence of increase in unscheduled DNA synthesis up to 100 mg/well - ≥ 333 **mg/well was cytotoxic. ACCEPTABLE. (Gee, 5/6/88).

****262-058 058404**, "In vitro Sister Chromatid Exchange in Chinese Hamster Ovary (CHO) Cells." (Pharmakon Research International, PH 319-RP-001-85, 4/23/86) Ethoprop, lot 304295001; tested without activation at 0, 5, 50, 100, 200 and 350 mg/ml and with activation, trial 1, at 0, 5, 15, 30, 50, 55 and 60 mg/ml and at 0, 50, 60, 65, 70 and 75 mg/ml in trial 2, 5 hours treatment followed by 29 additional hours of incubation; percent of cells in first, second and third mitoses were scored; 50 metaphases per concentration (25 from each culture) were scored for sister chromatid exchanges; no increase in SCE's were noted without activation; statistically significant increases were found in both trials in the presence of rat liver activation; **possible adverse effect**. ACCEPTABLE. (Gee, 5/6/88).

NEUROTOXICITY

262-004 962351, "Neurotoxicity Test - Hens - Technical VC 9-104 - Final Report," (Hazleton, 6/15/67). Ethoprop (assumed purity of 100%) tested at 5.62 mg/kg (ten hens), with TOCP (ten hens) positive controls and four negative control hens; UNACCEPTABLE, no individual observations, no redosing at 21 days when no signs of delayed toxicity were seen. Acute toxicity in that 4/10 died - inadequate number of hens. No adverse effect indicated. Atropine administered i.m. to hens in distress but these were not specifically identified. (Gee, 4/12/85).

EPA one-liner: Supplemental, negative effect.

**262-060 051509, "Acute Delayed Neurotoxicity Study with Ethoprophos in the Domestic Hen," (Huntingdon Research Centre, 8/6/86). Technical ethoprop, 94.5%, to 63 hens by oral gavage in corn oil at 6.5 mg/kg (= LD_{50} determined by lab) with repeat at 5.3 mg/kg on day 21, with positive control = TOCP at 500 mg/kg to 10 hens, and negative control = vehicle to 10 hens; with ethoprop, 70% mortality by day 4 in spite of atropine and/or 2-PAM protection (reason for reduction of second dose); no clinical signs of delayed neurotoxicity (locomotor ataxia); no evidence of nerve damage in 16 survivors examined microscopically. Complete and ACCEPTABLE, no adverse effect. (Martz, 6/25/87).

** 105 130418 "Acute Neurotoxicity Study with Ethoprop in Rats," (Weiler, M.S., Hazleton Wisconsin, Inc., Madison, WI; Laboratory Project ID: HWI 6224-200; 4/8/94). Ethoprop technical (96.2% pure) was administered by gavage in a single dose to Crl:CDBR VAF/plus rats (17/sex/dose) at 0 (corn oil) 5, 25 (females only), 50 and 75 (males only) mg/kg. Animals were observed and tested for 15 days post-dosing. NOEL = 50 mg/kg (males) and 25 mg/kg (females). Deaths occurred in both sexes at the high doses. Clinical signs were observed in males at ≥ 50 mg/kg and in females at ≥ 25 mg/kg during days 1-18 post-dosing. Male bodyweights were significantly decreased 8 days post-dosing. Both sexes showed effects from the FOB at ≥ 50 mg/kg in males and at ≥ 25 mg/kg at 2 hours post-dose. Motor activity was decreased

in males at ≥ 50 mg/kg and in females at 50 mg/kg. There were no macro or microscopic lesions observed which would indicate neurotoxicity. ChE NOEL < 5 mg/kg in both sexes (plasma and RBC) day 2 post-dosing. These effects were reversed and there were no effects observed in brain ChE when animals were tested at 15 days post-dosing. Acceptable. M. Silva, 1/25/95.

107 134404 "Acute Oral Gavage Study with Ethoprop in Rats: Time-related Effects of Ethoprop on Brain, Plasma, and Red Bood Cell Cholinesterase Activities," (Weiler, M.S., Project #: HWI 6224-209; Hazleton WI, Inc., Madison, WI; 9/23/94). Ethoprop technical (95.7% pure) was administered by gavage (1 dose) to Crl:CD(SD)BR VAF/Plus rats (24/sex/dose) at 0, 30 or 60 mg/kg (males) and 20 or 40 mg/kg (females). Acute Systemic NOEL = 30 mg/kg - males; no NOEL - females (One male was sacrificed moribund. Both sexes had lower bodyweights at the high doses. Males at 60 mg/kg and females at ≥ 20 mg/kg showed treatment-related clinical signs.) **Possible adverse effect:** A ChE NOEL was not achieved in either sex (Plasma, RBC and brain ChE were significantly decreased at all treatment levels by day 1. These effects showed signs of reversal at day 15 but were not completely reversed in RBC and brain.) These data are supplemental. M. Silva, 3/7/95.

** 106 134403 "13-Week Dietary Neurotoxicity Study with Ethoprop in Rats," (Weiler, M.S., Project ID: HWI 6224-199; Hazleton Wisconsin, Inc., Madison, WI; 9/21/1994). Ethoprop technical (95.7% pure) was fed in diet to Crl:CD BR VAF/Plus rats (27/sex/dose) at 0 (diet only), 4, 40 and 400 ppm for 13 weeks. Of the 27/sex/dose, 12/sex/dose were used for the FOB and 15/sex/dose were used for a ChE assay. Systemic NOEL = 40 ppm (At 400 ppm, both sexes showed decreased body weights. Food consumption was transitionally decreased in both sexes. Males at 400 ppm showed perianal brown haircoat that was test material related.) Neurotoxicity NOEL = 40 ppm (At 400 ppm, decreased capacity in the FOB (decreased mean analgesic reflex times, hindlimb grip strength in males) and motor activity tests were observed.) ChE NOEL < 4 ppm (ChE levels were decreased in RBC and Brain at ≥ 40 ppm throughout the study and in plasma at ≥ 4 ppm.) No adverse effects. Acceptable. M. Silva, 3/3/95.

108 134406 This volume is an exact copy of 105 130418, reviewed above.

IX. APPENDICES

APPENDIX A

OCCUPATIONAL EXPOSURE ASSESSMENT

ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA TO PESTICIDE PRODUCTS THAT CONTAIN ETHOPROP

by

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HS-1628 February 22, 1996

California Environmental Protection Agency
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Worker Health and Safety Branch
1020 N Street, Room 200
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SUMMARY

Ethoprop (Mocap®) is used in California against a variety of soil-borne nematodes and insects, primarily on potatoes and cabbage. The use of ethoprop in the state is being thoroughly evaluated since possible adverse effects have been found in animal studies including adenomas, hepatotoxicity, decreased fertility and chromosome and DNA damage.

During the years 1982 through 1988, no ethoprop related illness episodes were reported to the Department by physicians. In 1989, 11 illnesses, including one occupational and ten non-occupational illness cases, were reported. Most 1989 illnesses were either respiratory/allergic or systemic. Between 1989 and 1993, no new illness cases have been reported to the Department.

Ethoprop is rapidly metabolized in mammalian systems to at least eight metabolites. Of the metabolic products identified, O-ethyl S-propyl phosphorothioic acid should be found in the urine of humans in quantities large enough to allow biological monitoring.

The 24 hour dermal absorption rate has not been adequately assessed by the registrant, therefore 100 percent is assumed as a default. The relatively low absorbed dosages resulting from exposures already mitigated by labeling restrictions, and calculated in this fashion, could be further reduced by an accurate dermal absorption rate.

This report was prepared as Appendix A to the Department of Pesticide Regulation's risk assessment document for ethoprop.

APPENDIX A

California Department of Pesticide Regulation
Worker Health and Safety Branch

Human Exposure Assessment

ETHOPROP

February 22, 1996

INTRODUCTION

Ethoprop (Mocap®, ethoprophos, O-Ethyl S,S-dipropyl phosphorodithioate, $C_8H_{19}O_2PS_2$, CAS 13194-84-4) is a non-systemic cholinesterase inhibiting organophosphate nematicide/soil insecticide that kills pests by contact rather than through fumigant action. The pure chemical is a pale yellow liquid that is non-corrosive to metals. It is a semi-volatile organic compound with a vapor pressure of approximately 3.5×10^{-4} mm Hg. Ethoprop is somewhat soluble in water (700 ppm) and readily soluble in most organic solvents. It is very stable in neutral and weakly acid media (The Royal Society of Chemistry, 1987).

Ethoprop is a California and Federal Restricted Use Pesticide based on acute toxicity and hazard to birds. There are presently four formulations registered for use in California: Mocap® 10% granular, Mocap® 70% emulsifiable concentrate (EC) and Chipco Mocap® Brand 5G and 10G. California users of ethoprop can include producers of specific agricultural commodities such as potatoes, beans, corn and cabbages, and horticultural commodities, including turf, and caretakers of public and private turf areas including lawns, golf courses and cemeteries (Braun, 1988).

FEDERAL EPA STATUS

A Registration Standard was issued in June, 1983 that contains the U.S. Environmental Protection Agency's (EPA) regulatory position in regard to manufacturing use and end-use products containing ethoprop (U.S. EPA, 1986a). The primary concerns at the time of publication were potential avian hazard via treatment of grain or through granular formulations, retaining the restricted use classification for EC formulations containing over 40% active ingredient (a.i.) and that additional data be developed to complete the toxicity profile for ethoprop. Ethoprop was made a part of Data Call In Cluster One for corn, alfalfa and sorghum insecticides and the chronic data base for ethoprop was determined to be complete, for EPA purposes as of September, 1986 (U.S. EPA, 1986b).

USAGE

In 1993, 62,000 pounds active ingredient were reported used in California by Licensed Pest Control Operators and all other users of these restricted use compounds (Cal/EPA, 1994). In 1992, 41,000 pounds of ethoprop were reported to have been used (Cal/EPA, 1993). The use trend since the late 1980's has been upward. Use reports indicate that the majority of ethoprop reported used in California is applied to potatoes and cabbage (Cal/EPA, 1993). Secondary uses reported include turf and landscape maintenance. Other legal uses include bananas, several

varieties of beans and corn, cucumber, peanuts, plantain, potatoes and sweet potatoes, soybeans, sugarcane and tobacco.

No Mocap® formulations can be applied by aircraft. All applications must be mechanically incorporated and/or watered-in primarily from overhead irrigation. Irrigation can then be used to further move the pesticide into the soil. At present, ethoprop can be used for chemigation (Bireley, 1995). The 10% granular agricultural product can be applied in a row treatment, in a band over the row or by broadcast (label due to be registered Jan., 1996) while the turf 10% product can be broadcast (March, 1992 label). The emulsifiable concentrate can be applied in the same manner or through an irrigation system (May, 1995 label). The 5% granular product can be applied by hand using drop-type or similar spreaders but not chest or stomach-high grinder-type spreaders (June, 1990 label). The maximum application rate for the 10% granular products are 20 pounds of active ingredient per acre (a.i./acre) on turf and 12 pounds a.i./acre on potatoes and tobacco, while the maximum rate for the EC is 12 pounds a.i./acre for potatoes and tobacco. The maximum rate for the 5% granular is 30 pounds a.i./acre or 600 lbs of formulated product.

ILLNESS REPORTS

In the years 1982 to 1988 inclusive, no occupational or non-occupational illnesses were reported by physicians in California that were attributable to ethoprop (Mehler, 1995). In 1989, 11 illnesses were reported to the Department of Pesticide Regulation's (DPR) Pesticide Illness Surveillance Program, PISP (Mehler, 1995). One was to an incorporator in Siskiyou County who was using coveralls, goggles, gloves, boots and a dust-mask. Vomiting, queasiness and headache were the signs and symptoms reported. While the hospital stated laboratory tests, including cholinesterase (ChE), were inconclusive, it was indicated that the individual was probably "chemical sensitive". The illness was classified by DPR as systemic and probably related to exposure to ethoprop or its breakdown products. There was also a cluster illness in Siskiyou in 1989 that was reported to DPR that involved 10 people, at least one of which was a child. Signs and symptoms reported included exacerbated asthma problems, shortness of breath, stomach cramps, nausea, diarrhea, burning eyes and headaches. When tested, ChE levels were within laboratory normal range. Four cases were classified as respiratory and systemic, three as systemic only, two as respiratory only and one as an eye injury. All ten illnesses were categorized as possibly related to ethoprop or its break-down product. Between 1989 and 1993, no new cases were reported to PISP (Mehler, 1995)

The California Department of Health Services (CDHS) reported an illness case that does not appear to have been reported by physicians to DPR. This case involved an applicator near Dorris (also Siskiyou County) who was not wearing the required protective clothing. CDHS reports that the individual's employer failed to provide protective devices because of the expense involved (Mengle, 1991). In a published report (Ames and Stratton, 1991), CDHS described an incident where up to 421 individuals reported some type of illness. The application was made at 118 pounds of product per acre after seed potatoes were planted. CDHS epidemiologists investigated the incident because community residents sought medical attention due to odor-related illnesses. It is believed that this incident is the same as that above where 10 people were seen by physicians who reported to DPR. The most highly elevated 6-week health effects reported included headache, diarrhea, runny nose, sore throat, burning/itching eyes, fever, hay fever attacks and asthma attacks. CDHS concluded that these health effects were due to exposure to n-propyl-mercaptan, the primary, highly odorous and volatile break-down product.

WORK PRECAUTIONS

Present labels call for appropriate protective clothing and equipment. For the 10% granular products (the agricultural use label is updated for the Worker Protection Standard, WPS), which are in Toxicity Category II, "protective clothing" including rubber gloves is required along with a mask (sic) or pesticide respirator approved by MSHA/NIOSH. The label for the EC (Toxicity Category I) requires waterproof protective clothing, rubber gloves and goggles and specifies an example of a satisfactory approved respirator (also updated for the WPS). The 5% granular product (Toxicity Category II) requires protective clothing and rubber gloves and restricts the type of applicator to be used. All four labels require washing of hands, arms and face after use and laundering of clothing before reuse. Discarding of contaminated shoes is directed.

All four labels define symptoms of poisoning so that the user is more aware and could seek earlier treatment in the case of accidental over-exposure than if such statements were not present. It is believed that an awareness of potential adverse effects before use would avoid after the fact label searches for signs or symptoms of illness. Statements of Practical Treatment and Precautionary Statements for ingestion, skin or eye contact and notes to the physician are essentially the same on each label.

After application, reentry by field workers or others into treated areas is prohibited in California until the product has been incorporated into the soil. The agricultural products have reentry intervals of 48 to 72 hours depending upon average rainfall in the location applied. Even if not a part of the application process, the incorporator must wear the same protection as application personnel.

DERMAL ABSORPTION

One dermal absorption study has been submitted by the registrant (Stoughton, 1986). It was an <u>in vitro</u> study conducted at the University of California at San Diego in December of 1986. Human cadaver skin and "fresh skin" from the mouse, rat and rabbit were used. In each case, underlying fascia and fat was removed. The test material was Mocap® EC ([1^{-14}C-propyl] ethoprop) in hexane with a specific activity of 1.6 mCi/mmol. Mocap® EC and the same material diluted with 19 parts distilled water were applied to each test species. A dose of about 1.27×10^6 counts per minute was applied in each 0.02 cc dose to each skin sample.

The skin samples were glued over specifically prepared wells containing 10 cc of normal saline with the epidermis facing out and the dermal side bathed in the saline. At seven sampling times covering 24 hours, two cc of the saline were collected for counting. After each sample was collected, the two cc of saline were replaced with fresh saline. Sampling and replacement were accomplished through an outlet designed into the sample vessel.

The following results were reported:

Table 1-Percent Penetration[a]
(Cumulative Percent of Total Dose)

Test	1 hour		6 hours		24 hour	
Species	EC	Dil. EC	EC	Dil. EC	EC	Dil. EC
human	0.0008	0.08	0.08	1.10	1.00	5.20
rabbit	0.04	0.20	1.52	7.70	7.84	27.40
mouse	0.11	1.90	5.00	29.00	16.20	37.80
rat	0.15	0.55	1.70	7.85	5.40	22.65

[a] Stoughton, 1986

At present, skin penetration data developed in vitro is not acceptable without explanation of the method's relevance to absorption in living human systems. The ratio of oral to dermal LD_{50} in the rat (17%) suggests that the in vitro dermal data may be a valid indicator of dermal absorption for the rat. Further bridging data defining the relationship between in vitro vs. in vivo measurement in the test species reported is required, but is missing here. In the absence of such data, 100 percent dermal absorption in 24 hours exposure will be used for the exposure assessment.

CHOLINESTERASE RESPONSE

A dermal dose red cell cholinesterase (ChE) response study was conducted in 1986 under a cooperative agreement between the registrant, the California Department of Health Services and the Laboratory for Energy-Related Health Research of the University of California (Knaak, et al., 1986a). A comparison of cholinesterase inhibition was made between technical ethoprop with ethyl parathion as a positive control (both applied in 0.5 ml acetone) and Mocap® 6 EC (applied in water). The dose was applied to the clipped backs of male albino rats weighing between 266 and 313 grams and spread with a glass rod. The animals were exposed for a period of 72 hours. During the exposure period, the application site was not covered, but grooming was prohibited by a Queen Anne collar made from polyethylene sheeting. At the end of the exposure period, the animals were anesthetized with sodium pentothal and blood was obtained by cardiac puncture. The blood was analyzed colorimetrically for Red Blood Cell (RBC) cholinesterase activity and the data was treated statistically after the methods of Knaak et al. (1980).

RBC ChE response data has been used previously to estimate the risk to applicators of organophosphates (Knaak, et al., 1986b). After rat study data has been interpreted to establish a dermal dose-ChE response curve, an acceptable No Observable Effect Level (NOEL) for ChE inhibition in humans can be estimated. As such, the effective dose ED_{10} value is assumed to be below the point at which clinical signs of ChE inhibition can be detected. The ED_{10} was extrapolated at ten percent from a straight-line equation of the log dose vs. probit inhibition value. To extrapolate from the rat data to humans, a comparison of the surface areas exposed was used. Safety factors of from 10 to 100 ($NOEL/ED_{10}$) were then included in the final interpretation.

In the subject study, application of the above safety factors gave 0.05 to 0.5 $\mu g/cm^2$ as safe doses to the skin resulting from dermal exposure for the EC or technical products. These figures

translate to whole body dosages of 1 to 10 mg/person/day, depending upon the safety factor employed, that would not be expected to cause biologically significant cholinesterase inhibition.

METABOLISM

One study published in the open literature was available for review of ethoprop metabolism (Iqbal, 1972). Metabolism was investigated in vivo in the rat via urine and in vitro in liver microsomes of rat and rabbit. At least eight metabolites were identified; most transformations were the result of deethylation and depropylation of the molecule. An initial metabolic product was a transient propyl thiolate ion. Ethoprop was reportedly completely metabolized in the rat within six hours.

Of the metabolic products found, O-ethyl S-propyl phosphorothioic acid was found in the urine in quantities large enough (36% to 44% of the administered dose within 24 hours) to be useful for biological monitoring.

WORKER EXPOSURE

Four worker exposure study reports have been submitted by the registrant that cover exposure scenarios involving the EC. Included are data for the work activities of mixing, loading and applying with and without incorporation (mechanically burying the pesticide in the soil by turning over or mixing the top few inches of soil), as well as post-application incorporation (when the incorporation equipment is not managed by the applicator) and post-incorporation irrigation (normally an overhead irrigation that occurs once the applicator has left the field). Exposure to the granular products has been evaluated using surrogate data as no data were provided by the registrant.

The first study submitted by the registrant was conducted in May, 1981, northeast of Salinas, California (Popendorf and Cohen, 1984). Mocap® 6 EC was mixed in a closed system and then applied at six pounds of active ingredient per acre in 60 gallons of water per acre by low horizontal boom. One worker was monitored for potential dermal and inhalation exposure during mixing/loading and separately during application. Also, air samples were collected in the breathing zone of a driver of incorporation equipment and in the ambient downwind air at the application site. Traditional cloth patch dosimetry was used to measure potential exposure outside of clothing, inside cotton polyester coveralls and inside a rubberized rainsuit and street clothing at the skin. Hand exposure was measured using fruit pickers gloves as dosimeters under protective rubber gloves. Potential inhalation exposure was measured using filter cassettes and sorbent tubes attached to personal pumps set at 1.5 liters per minute.

Measured potential dermal exposure outside protective clothing during mixing/loading was 14.1 milligrams per hour (mg/hr), during the two hours of monitoring, which did not include exposure to the hands. During application, potential exposure was found to be 4.2 mg/hr. This approximates 110 mg/8 hr day for mixing/loading and 34 mg/8 hr day for application, without including potential hand exposure. Inside the rainsuit and street clothing, measured exposure including the hands (as protected by rubber gloves) during mixing and loading and application was 0.55 mg/hr. Excluding exposure to the head and hands, measured exposure inside the rainsuit and street clothing totaled 0.39 mg/hr, also during mixing/loading and application.

Potential inhalation exposure was found to be 2.4 micrograms/hour (µg/hr) during mixing/loading, 1.3 µg/hr during application and 1.7 µg/hr as a time weighted average (TWA) of

the two work tasks. During incorporation, ambient exposure was found to be 7.21 µg/m^3, and compound found in the ambient air during 2.5 hours beginning near the end of application was 2.5 µg/m^3.

In a second single worker study, with application characteristics and monitoring methods almost identical to the first, a mixer/loader-applicator (M/L/A) received a TWA of 37.6 mg/hr potential exposure outside of all clothing with hand values included (Popendorf et al., 1984a). This translates to 300 mg/day without the benefit of any protection from clothing. By wearing coveralls with street clothing and rubber gloves, this figure was reduced to 0.6 mg/hr or 5 mg/day. This result compares favorably with the 0.55 mg/hr rate found in the first study beneath the rainsuit and street clothing, although more protection was used in the first. For mixing/loading only, without hand exposure, 225 mg/8 hr day was measured. For application only, also excluding hands, the number is 22 mg/8 hr day outside the coveralls. Hand exposure was measured using glove dosimeters as in the first study.

Potential inhalation exposure was determined to be 15 µg/hr as a TWA for mixing/loading-application. For loading, less than 0.2 µg/hr was found. During application, the dose rate was 19 µg/hr. While the dose rate during mixing/loading was lower, the dose rates for application and for the TWA were considerably higher than study one. This second study is supportive of the order of magnitude of exposures found in the first study, however, the dermal exposures found were not measured with protection from a rainsuit which is currently required on the EC label.

The third study was carried out in conjunction with the first two studies near Salinas, and additional monitoring was conducted near Lodi, CA (Popendorf et al., 1984b). The monitoring included ancillary reentry activities and involved two cultivators and three irrigation workers. Monitoring was by methods as described in the two previous studies. Application was by low boom followed by incorporation accomplished by a combination spring-tooth harrow, spike tooth harrow and ring roller. The study investigators expect that this incorporation method represented an extreme case for dustiness. The application rates ranged from five to six pounds a.i./acre. Irrigation monitoring was accomplished with workers simulating the activities of field workers.

Potential exposure for each of the activities monitored was low. Air concentrations of ethoprop in the breathing zone of the cultivators ranged from 7.2 to 48 µg/m^3. Potential exposures outside protective clothing when head and hand exposures were included were calculated to be 9.5 mg/hr using dose density data to extrapolate from measured patches to unmeasured areas of the body. For irrigators, the breathing zone was determined to contain from <0.07 to 8 µg/m^3. Potential dermal exposure outside clothing ranged from <0.9 to <4.0 µg/hr not including hands. Hand exposures as measured using solvent rinsing of butyl rubber gloves ranged from six to seven µg/hr while handling irrigation pipe.

A fourth study conducted in 1986 in the Salinas Valley was submitted (Leffingwell, 1986). Measurements were made of exposure to heads and hands only of four workers mixing/loading and applying Mocap® EC at rates ranging from 9.5 to 13 pounds a.i./acre. Incorporation was part of the application process. Blood was drawn daily for measurement of cholinesterase activity. Cholinesterase monitoring was to be the major method of exposure evaluation. In this study, an average of 15 percent of the time monitored was during the loading operation while 85 percent was during application.

Cholinesterase monitoring consisted of blood drawing and analysis at Salinas Clinical Laboratories which is a licensed clinical laboratory that regularly performs ChE analysis. Both red-cell and plasma ChE tests were completed. Three pre-exposure samples were collected from each participant. The average of these three samples was considered the individual's baseline with at least one sample collected the first day of exposure (with one exception). Post-exposure samples were collected as soon after exposure as possible, which in all but two cases was within two hours after exposure.

Clothing worn by the study participants critically impacted the cholinesterase monitoring. Each participant was identically dressed as follows: clean long-sleeve twill work shirts and denim jeans daily, heavy twill coveralls over the shirts and jeans, a new pair of rubber boots issued at the beginning of the study. Rubber gloves and disposable respirators were changed daily. Face shields and hard hats were provided for mixing/loading.

Exposure to hands was measured in a mixture of 2-propanol and water. Left and right hands were washed separately. No indication was given for how long the hands were in the alcohol-water solution. Exposure to the head, face and neck was evaluated by attaching a single gauze pad in a Mobay-type holder to a cap worn by each individual. No breathing zone air monitoring was conducted in this study.

Results indicated low exposures. The average for hands was 6.3 µg/hr. Extrapolated head, face and neck exposures averaged 33.7 µg/hr. Of the 13 red-cell ChE values, five demonstrated statistically insignificant changes in respect to baseline with a range of -7.3 to + 5.1 percent. For the plasma samples, 10 of thirteen showed no significant changes compared to baseline (range -8.9 to + 7.9 percent). No changes were greater than two standard deviations from the baseline means leading the investigators to conclude that there was no biologically significant change in cholinesterase values.

The first three cited worker exposure studies do not meet EPA guidelines (Subdivision U) for studies submitted to support registrations. Missing are such critical attributes as field and storage control data and recoveries, sample calculations and related assumptions and raw data. The studies were, however, conducted under the auspices of and/or protocol review by DPR. Overall quality is approximately equivalent to studies conducted by the Worker Health and Safety Branch during the same time period. Aside from these, no other data are available that measure ethoprop EC exposure. With the possible exception of the irrigator data, the studies support each other with regard to order of magnitude. The irrigator data is not considered complete as in some cases workers were only monitored below the waist plus the hands. Only uncontaminated pipe was handled during the study. It is with these caveats that the EC study data are presented in Tables 2 and 3.

A study found in the open literature that measured exposure to a low percent a.i. granular product (Weiskopf et al, 1988) is suitable for estimating exposure to the 5% granular ethoprop. In this study, 14 replications of loading/applying a 14% Diazinon product used for Japanese Beetle eradication were monitored. These 14 did not use a "belly grinder" but used two drop type spreaders or a coffee can with holes for treating shrubs. This coffee can type of application can be ignored since the 5G label does not allow this use. Each worker was required by the employer to wear disposable polyethylene coveralls, rubber boots and rubber gloves. In order to use this data, the differences in application rate and percent active ingredient in the formulated product must be factored in. The exposure data were therefore multiplied by a factor of 5.4.

Potential respiratory exposure was measured using conventional air sampling pumps set to draw 1 liter per minute through an XAD-4 resin tube. Hands and wrists were washed with 100 ml of ethyl alcohol. Patches were attached on the outside of the coveralls on the right and left chest and the center of the back at the neck line. Patches were also placed at the top front of the right and left boot under the coveralls. Urine samples were collected at the beginning and end of the work day (3.3 to 7 hours) to measure the metabolite DETP (diethylthiophosphate). Urine sample analytical results were normalized for creatinine excretion.

As no data were available for estimating exposures for the 10G product, a suitable surrogate was found (Devine et al.,1986). Turbufos, sold as Counter® 15G, was applied at 8 ounces a.i./1000 ft of row (approximately 8 lbs/acre) for 11 replicates of exposure monitoring via essentially the same equipment as an ethoprop 10G would be made. Because the application methods would be almost identical and the percent a.i., acute toxicity and the vapor pressure are so similar, this data can be used with only a normalization for percent a.i. A multiplier of 0.66 was used. All data were used with this minor correction.

The quality of this study was high. Methods used, validations and quality control would meet current standards. Dermal exposure was measured by using the Durham and Wolfe patch method and respiratory exposure was measured using XAD-2 sorptive tubes and personal pumps set at 1.5 liters/minute. Total 24 hour urine samples found no detectable level of dialkylphosphate metabolites and plasma and RBC ChE monitoring found no significant difference in activity when compared to pre-exposure values or controls.

Also available was a soil dissipation study conducted in Washington state (Cooley et al., 1991). The EC and the 10G formulations were followed from planting to harvest for a total of over 176 days for a potato crop in the Columbia Basin. When applied at 12 lbs active ingredient per acre, and sampled to a depth of less than one centimeter, both formulations had a half life of 22 days. The only time residue levels were significantly different was at day 0 when the EC level was 0.125 g/cm^2 and the 10G level was 0.042 $\mu g/cm^2$. Another important point from this study is that at each time the soil was disturbed (dragoff, hilling and harvest) the residue level doubled from that detected pre-event indicating disturbance brought the material to the surface.

Table 2- Measured and Calculated Inhalation and Dermal Exposures to Application and Reentry Personnel as Estimated for an Eight Hour Day for the Emulsifiable Concentrate, 5G and 10G Formulations of Ethoprop

Worker	Dermal Exposure (µg/hr) Head,Hands,Body			Potential Exposure (µg/hr)	Tot. Dermal Exposure[e] (µg/hr)	Potential Inhalation[f] (µg/hr)	Total Exposure 8 hr/d[g] (mg)
M/L/A(EC) (N=1)	34[a]	6[a]	390[b]	4300 est.	430	15	3.6
Incorp.(EC) (N=1)	-	-	-	9500[c]	950	48	7.9
Irrig.(EC) (N=3)	-	-	-	11[d]	1	8	0.07
Load/Apply /Incorp. Hand(5G) (N=10)	-	-	-	270[h]	27	16	0.2
Load/Apply /Incorp. Ground(10G) (N=11)	16	5	225[i]	246	25	7	0.3

Meinders, WH&S, 1996

[a] Hand and head exposure measured inside waterproof rubber (sic) gloves and by gauze pad attached to hat, respectively; incorporation was part of the application process (Leffingwell, 1986).

[b] Dermal exposure measured inside coveralls and rainsuit via gauze pads on street clothing (Popendorf and Cohen, 1984). Order of magnitude supported by (Popendorf *et al*., 1984a).

[c] Dermal exposure during incorporation measured outside protective clothing, and it is assumed under protective gloves (Popendorf *et al*., 1984b).

[d] Dermal exposure during irrigation measured outside protective clothing and inside rubber boots. Hand exposure measured via solvent rinsing of butyl rubber gloves (Popendorf *et al*., 1984b).

[e] Protected exposure inside protective clothing and equipment.

[f] Potential inhalation exposure measured in breathing zone outside respirator; (Popendorf *et al*., 1984a: M/L/A) and (Popendorf *et al.*, 1984b: incorporation and irrigation).

[g] Total protected dermal plus potential inhalation exposure.

[h] Includes rotational periods of using a belly grinder. Hands protected by rubber gloves. Body estimate based on leg exposure as protected by coveralls multiplied by 10 fold protection factor.

[i] Body protected by coveralls multiplied by 10 fold protection factor, head and hands unprotected for this study.

Table 3-Estimated Dermal and Inhalation Exposure and Calculated Annual and Lifetime Average Daily Dosages Based on CDPR Extrapolations of Cited Exposure Measurements

Worker	Dermal Exposure[a] (mg/8 hr/day)	Inhalation Exposure[b] (µg/8 hr/day)	Absorbed Daily Dosage[c] (µg/kg/day)	Time Worked[d] (day/yr)	AADD[e] (µg/kg/day)	LADD[f] (µg/kg/day)
M/L/A(EC)	3.4	12	62	10	1.7	1.0
Incorp.(EC)	7.6	38	139	10	3.8	2.2
Irrig.(EC)	0.01	6.4	0.2	20	0.01	0.01
Load/Apply Incorp. Hand(5G)	0.2	125[g]	5	20	0.3	0.2
Load/Apply Incorp. Ground(10G)	0.3	5.9	4.7	10	0.1	0.07

Meinders, WH&S, 1996

[a] From Table 1, not including potential inhalation exposure.
[b] Potential inhalation exposure from Table 1, reduced by 90% protection of respirator.
[c] Dermal plus inhalation/54.8 kg (based on surface areas used) assuming 50% uptake of lung dose and 100% absorption of dermal dose.
[d] 10 days/year estimate based on low volume of product reported used each year with one application period per year. Irrigators have the potential for greater time in treated areas. 5G estimate base on 5 month potential application period and 1 day/week. 10G based on EC estimate.
[e] Annual Average Daily Dosage = Absorbed Daily Dosage x days exposed/365 days per year.
[f] Lifetime Average Daily Dosage = AADD x 40 years/70 year lifetime.
[g] Not reduced by respiratory protection.

EXPOSURE APPRAISAL

The science of risk assessment is filled with uncertainty, and the risk assessor tends to be very conservative when making the numerous assumptions that are inherent in the process. It is incumbent upon the risk assessor to openly and honestly discuss the sources of uncertainty so that the risk manager can put them in perspective. The best risk estimates are made with lots of high quality data. Unfortunately in the case of many chemicals such data is sadly lacking.

There are several factors in most exposure assessments that make them very conservative. Even with "reasonable" input parameters for exposure calculation, there is a high degree of conservatism (tendency to overestimate exposure) not immediately apparent. These factors are very real, but typically hidden and therefore not acknowledged. Below is a brief narrative on the most important factors that produce overestimates.

Dermal versus Oral Plasma Levels

Dosage is expressed as a single static value both in worker exposure and animal toxicology studies. The rate of dermal absorption is always lower than the rate of oral absorption in animals used for toxicology testing. Adverse effects occur only when plasma levels in the target organ exceed a critical level. However, dermal acquisition occurs over the entire work day, and because dermal absorption is slower than oral, plasma levels for the same total absorbed dosage will not be nearly as high for a dermal versus oral exposure. A dermal dose acquired over the entire workday produces peak plasma levels much lower than the bolus oral feeding dosage acquired by animals

in seconds to minutes. Because effect is highly dependent on plasma level, treating an eight hour dermal acquisition as though it were a bolus (i.e., summing the entire dermal dose) is so conservative that it outweighs any other perceived source of underestimating exposure. The net effect of assuming instantaneous dermal dose acquisition and absorption is an overestimate of peak plasma concentration compared to the oral route by several fold for the same absorbed dose (Auton et al., 1993). Note that the lower the dose, the more pronounced this difference becomes. This difference is particularly pertinent when comparing the doses used in a toxicology study versus those to which a human would be exposed.

Lower urinary metabolite concentrations (an indication of lower peak plasma concentrations) are also seen with dermally applied pesticides when compared with the urinary metabolite concentration observed following oral dosing (Krieger et al., 1991).

Short Workday Exposure Monitoring Overestimates Full Day

Another source of overestimated dose comes from partial day monitoring. Spencer et al., (1995) report that if an estimate of full day exposure were extrapolated from 1/3 day (four bins picked) the exposure would be overestimated by more than 50 - 80% and from 1/2 day (six bins picked) 20 - 40%. Shorter monitoring periods are encouraged because it allows an investigator to obtain two or more replicates per individual per day of monitoring. Hand residues were found to remain virtually constant indicating that they rapidly come into equilibrium with their environment. Thus summing hand washes taken throughout the day grossly overestimates actual dose.

This same principle is operative for pesticide handler exposure monitoring studies. The ungloved hand is typically the source of highest potential exposure for handlers (Fenske, 1993). Three important factors produce high exposure estimates for handlers. One is the tendency of passive dosimetry to overestimate dermal dose (Maddy et al., 1989; Spencer et al., 1995). The second is the influence of serial hand washes (the same factor operating in reentry worker exposure). Finally the dermal dose to hands produces high concentrations on hands and leads to reduced percent dermal absorption (see next section).

PHED Modeling and Other Patch Dosimetry Methods

The Pesticide Handlers Exposure Database (PHED) utilizes almost exclusively patch dosimetry. This dosimetry method was introduced by Durham and Wolfe (1962) as a means of estimating dermal exposure for workers exposed to pesticides. This monitoring method typically overestimates exposure compared to other methods of exposure monitoring as indicated above. There are a number of reasons for such overestimates, but one in particular is operating in virtually every study. Approximately half of the data points for dermal monitoring in PHED and most patch dosimetry studies are non detects. Because a majority of the studies in the database are more than 10 years old, many of the detection limits are $>0.1 \mu g/cm^2$. The net effect is that an unmeasured residue below the detection limit is a major component of the exposure because we use 1/2 the limit of detection when there are non detects. Assuming a body surface of 20,000 cm^2 and the $0.1 \mu g/cm^2$ detection limit, the estimated exposure if all patches were non detects would be 1000 µg.

Dermal Absorption: Animal > Human

Skin is the primary route of worker exposure (Wolfe, 1976) accounting on average for 99% of the potential pesticide exposure for pesticide handlers. As a result, another significant factor that contributes to overestimation of dose is the difference between animal and human dermal absorption. The rat is the most commonly used model to estimate dermal absorption. This is

because rats are relatively cheap and most of the toxicology is done with them. Also many companies have an aversion to using humans for the determination of dermal absorption, even though they are the species for which risk assessment is intended. However, the rat typically overestimates human dermal absorption by two to ten fold. This has been demonstrated in approximately a dozen different compounds tested in both rats and man (Wester and Maibach, 1977; Shah and Guthrie, 1983; Wester and Maibach, 1993; Feldman and Maibach, 1974; Sanborn, 1994; Thongsinthusak, 1994). For ethoprop, the available data suggest that the default 100% dermal absorption overestimates absorption by approximately five fold.

Percent Bioavailability

Percent bioavailability of a dermal dose of some chemicals declines with increasing concentration (Wester and Maibach, 1976). Some regions of the body receive disproportionate amounts of exposure (e.g., the hands which constitute 8% of the body surface area receive up to 50% or more of the total dermal exposure; Spear et al., 1977 for harvesters; and Maddy et al., 1984 for mixer loaders) and as a result experience higher concentration of pesticide than other body regions. However, the hands are assumed to have the same rate of absorption despite the much higher concentration thus typically overestimating absorbed dose by a factor of two. Although dermal absorption varies by body region (Maibach, et al., 1971) the highest absorption regions tend to experience the lowest exposure due to protected anatomical locations (e.g., ear canals, testicles and armpits), and the most exposed body areas differ by less than three fold in absorption rate. Further the forearms are typically tested for absorption in a human study, and this region falls in the middle of the range for rate of absorption compared to the other body areas normally exposed to pesticides.

The mean rat dermal absorption for 26 pesticides from several different chemical classes was 19%±16% (Thongsinthusak et al., 1993). Thus at the 95th percentile, dermal absorption for pesticides in general would be 51%. This indicates that when we assume 100% dermal absorption in the absence of data, the overestimate of absorbed dose will be at least two fold.

Conclusion About Exposure Estimates

These five factors are operative in this exposure assessment and because they are multiplicative, they could result in overestimates of eight or more fold. The concern that the maximally exposed individual is not adequately represented by mean estimates of exposure is not well founded when considering all the "hidden" conservatism built into all estimates of exposure resulting from the dermal route.

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APPENDIX B

USEPA Tolerances for Ethoprop

0.02(N) Bananas
0.02(N) Beans, Lima
0.02(N) Beans, Lima, Forage
0.02(N) Beans, Snap
0.02(N) Beans, Snap, Forage
0.02(N) Cabbage
0.02(N) Corn, Fodder (Incl. Field Corn & Sweet Corn)
0.02(N) Corn, Forage (Incl Field Corn & Sweet Corn)
0.02(N) Corn, Fresh (Includes Sweet Corn, K+CWHR)
0.02(N) Corn, Grain
0.02(N) Cucumbers
0.02 Mushrooms
0.02(N) Okra
0.02(N) Peanuts
0.02(N) Peanuts, Hay
0.02(N) Pineapples
0.02(N) Pineapples, Fodder
0.02(N) Pineapples, Forage
0.02(N) Potatoes
0.02(N) Soybeans
0.02(N) Soybeans, Forage
0.02(N) Soybeans, Hay
0.02(N) Sugarcane
0.02(N) Sugarcane, Fodder
0.02(N) Sugarcane, Forage
0.02(N) Sweet Potatoes

APPENDIX C

Acute Dietary Exposure Analyses and Residue File

ACUTE EXPOSURE ANALYSIS (EX4) FOR ethoprop Section 3 Registration
RESIDUE FILE NAME: ETHA Analysis Date: 8-31-93
DPR NOEL = 2.0 mg/kg-day
COMMENT 1: Values equal to the USEPA tolerances
COMMENT 2: All label-approved uses for ethoprop

RESIDUE FILE LISTING

TAS CODE	EPA CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ #1	FCTRS #2	SOURCE CODE
71	06002AA	A	BANANAS-OTHER VARIETIES	no consumption in survey			
72	06002AB	A	BANANAS	0.020000	1.00	1.00	EPA
73	06002DA	A	BANANAS-DRIED	0.020000	3.90	1.00	EPA
89	06013AA	A	PINEAPPLES-PEELED FRUIT	0.020000	1.00	1.00	EPA
90	06013DA	A	PINEAPPLES-DRIED	0.020000	0.00	1.00	EPA
91	06013JA	A	PINEAPPLES-JUICE	0.020000	1.70	1.00	EPA
148	10010AA	J	CUCUMBERS	0.020000	1.00	1.00	EPA
170	13007AA	F	CABBAGE-GREEN AND RED	0.020000	1.00	1.00	EPA
173	13010AA	F	CABBAGE-CHINESE/CELERY/BOK CH	0.020000	1.00	1.00	EPA
207	14013AA	B	POTATOES(WHITE)-WHOLE	0.020000	1.00	1.00	EPA
208	14013AB	B	POTATOES(WHITE)-UNSPECIFIED	no consumption in survey			
209	14013AC	B	POTATOES(WHITE)-PEELED	0.020000	1.00	1.00	EPA
210	14013DA	B	POTATOES(WHITE)-DRY	0.020000	6.50	1.00	EPA
211	14013HA	B	POTATOES(WHITE)-PEEL ONLY	0.020000	1.00	1.00	EPA
218	14018AA	B	SWEET POTATOES (INCLUDING YAM	0.020000	1.00	1.00	EPA
229	15001AC	G	BEANS-DRY-LIMA	0.020000	1.00	1.00	EPA
233	15002AA	G	BEANS-SUCCULENT-LIMA	0.020000	1.00	1.00	EPA
235	15003AB	G	BEANS-SUCCULENT-OTHER	0.020000	1.00	1.00	EPA
237	15004AA	O	CORN/POP	0.020000	1.00	1.00	EPA
238	15005AA	O	CORN/SWEET	0.020000	1.00	1.00	EPA
239	15006AA	A	PEANUTS-WHOLE	no consumption in survey			
245	15015AA	A	OKRA	0.020000	1.00	1.00	EPA
255	15029AA	G	SOYBEANS-SPROUTED SEEDS	0.020000	0.33	1.00	EPA
261	16003AA	A	MUSHROOMS	0.020000	1.00	1.00	EPA
266	24002EA	O	CORN/GRAIN-ENDOSPERM	0.020000	1.00	1.00	EPA
267	24002HA	O	CORN/GRAIN-BRAN	0.020000	1.00	1.00	EPA
268	24002SA	O	CORN SUGAR	0.020000	1.50	1.00	EPA
283	25003SA	A	CANE SUGAR	0.020000	1.00	1.00	EPA
289	27002OA	O	CORN GRAIN-OIL	0.020000	1.00	1.00	EPA
293	27007OA	A	PEANUTS-OIL	0.020000	1.00	1.00	EPA
297	27010OA	G	SOYBEANS-OIL	0.020000	1.00	1.00	EPA
303	15023AA	G	SOYBEANS-UNSPECIFIED	0.020000	1.00	1.00	EPA
304	28023AB	G	SOYBEANS-MATURE SEEDS DRY	0.020000	1.00	1.00	EPA
305	28023WA	G	SOYBEANS-FLOUR (FULL FAT)	0.020000	1.00	1.00	EPA
306	28023WB	G	SOYBEANS-FLOUR (LOW FAT)	0.020000	1.00	1.00	EPA
307	28023WC	G	SOYBEANS-FLOUR (DEFATTED)	0.020000	1.00	1.00	EPA
378	06002NA	A	BANANAS-NECTAR	0.020000	1.00	1.00	EPA
383	13007SA	F	CABBAGE-SAVOY	no consumption in survey			
388	24002MO	O	CORN SUGAR-MOLASSES	0.020000	1.50	1.00	EPA
403	15006BT	A	PEANUT-BUTTER	0.020000	1.89	1.00	EPA
406	06013JC	A	PINEAPPLES-JUICE-CONCENTRATE	0.020000	6.30	1.00	EPA
911	NOCODE	A	MOLASSES-NFS	0.020000	1.00	1.00	EPA
940	NOCODE	A	PEANUTS HULLED	0.020000	1.00	1.00	EPA

ACUTE EXPOSURE ANALYSIS (EX4) FOR Ethoprop — Section 3 Registration
RESIDUE FILE NAME: ETHA — Analysis Date: 8-31-93
DPR NOEL = 2.0 MG/KG BODY WT/DAY
COMMENT 1: Values based on tolerances
COMMENT 2: All label-approved uses for ethoprop

U.S. POP - ALL SEASONS

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MARGIN OF SAFTEY
99.8%	0.000077	26108

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000014	142122	20.0	0.000115	17452
80.0	0.000025	80106	10.0	0.000159	12607
70.0	0.000035	56732	5.0	0.000221	9034
60.0	0.000046	43691	2.5	0.000286	6998
50.0	0.000056	35410	1.0	0.000381	5248
40.0	0.000070	28672	0.5	0.000468	4272
30.0	0.000086	23146	0.0	0.002299	870

WESTERN REGION

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MARGIN OF SAFTEY
99.7%	0.000071	28211

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000012	160096	20.0	0.000109	18278
80.0	0.000023	87282	10.0	0.000147	13587
70.0	0.000033	61074	5.0	0.000198	10107
60.0	0.000043	46470	2.5	0.000255	7856
50.0	0.000054	37325	1.0	0.000329	6070
40.0	0.000067	29676	0.5	0.000385	5192
30.0	0.000084	23886	0.0	0.000961	2081

ACUTE EXPOSURE ANALYSIS (EX4) FOR Ethoprop — Section 3 Registration
RESIDUE FILE NAME: ETHA — Analysis Date: 8-31-93
DPR NOEL = 2.0 MG/KG BODY WT/DAY

HISPANICS

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.3%	0.000078	25689

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000011	185501	20.0	0.000114	17587
80.0	0.000020	98996	10.0	0.000163	12246
70.0	0.000031	64445	5.0	0.000240	8336
60.0	0.000042	48043	2.5	0.000330	6066
50.0	0.000052	38464	1.0	0.000530	3777
40.0	0.000065	30726	0.5	0.000752	2661
30.0	0.000083	24116	0.0	0.001084	1844

NON-HISPANIC WHITES

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.8%	0.000076	26332

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000014	139301	20.0	0.000114	17559
80.0	0.000025	79082	10.0	0.000156	12854
70.0	0.000036	56208	5.0	0.000217	9232
60.0	0.000046	43413	2.5	0.000281	7109
50.0	0.000057	35292	1.0	0.000371	5393
40.0	0.000070	28632	0.5	0.000455	4397
30.0	0.000086	23171	0.0	0.002299	870

ACUTE EXPOSURE ANALYSIS (EX4) FOR Ethoprop — Section 3 Registration
RESIDUE FILE NAME: ETHA — Analysis Date: 8-31-93
DPR NOEL = 2.0 MG/KG BODY WT/DAY

NON-HISPANIC BLACKS

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.7%	0.000081	24770

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000014	145759	20.0	0.000121	16566
80.0	0.000024	82239	10.0	0.000179	11188
70.0	0.000034	58571	5.0	0.000257	7784
60.0	0.000044	45301	2.5	0.000325	6152
50.0	0.000055	36073	1.0	0.000418	4790
40.0	0.000068	29235	0.5	0.000486	4113
30.0	0.000088	22767	0.0	0.001617	1237

NON-HISPANIC OTHER

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.6%	0.000076	26427

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000013	153747	20.0	0.000110	18194
80.0	0.000028	72169	10.0	0.000149	13419
70.0	0.000042	48179	5.0	0.000213	9406
60.0	0.000050	39973	2.5	0.000286	6994
50.0	0.000059	34155	1.0	0.000371	5398
40.0	0.000070	28490	0.5	0.000421	4750
30.0	0.000085	23570	0.0	0.000712	2807

ACUTE EXPOSURE ANALYSIS (EX4) FOR Ethoprop — Section 3 Registration
RESIDUE FILE NAME: ETHA — Analysis Date: 8-31-93
DPR NOEL = 2.0 MG/KG BODY WT/DAY

NURSING INFANTS (<1 YEAR)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
96.1%	0.000099	20154

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000011	180049	20.0	0.000162	12323
80.0	0.000017	117029	10.0	0.000355	5629
70.0	0.000022	92645	5.0	0.000418	4783
60.0	0.000026	76670	2.5	0.000450	4449
50.0	0.000044	45043	1.0	0.000468	4270
40.0	0.000058	34716	0.5	0.000481	4161
30.0	0.000115	17345	0.0	0.000494	4049

NON-NURSING INFANTS (<1)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.1%	0.000170	11732

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000028	71672	20.0	0.000286	6986
80.0	0.000039	50942	10.0	0.000457	4376
70.0	0.000055	36229	5.0	0.000599	3337
60.0	0.000075	26499	2.5	0.000670	2983
50.0	0.000102	19644	1.0	0.000853	2346
40.0	0.000145	13794	0.5	0.000996	2007
30.0	0.000201	9927	0.0	0.001364	1466

ACUTE EXPOSURE ANALYSIS (EX4) FOR Ethoprop — Section 3 Registration
RESIDUE FILE NAME: ETHA — Analysis Date: 8-31-93
DPR NOEL = 2.0 MG/KG BODY WT/DAY

FEMALES (13+/PREG/NOT NSG)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.6%	0.000056	35958

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000012	170062	20.0	0.000089	22501
80.0	0.000022	89526	10.0	0.000105	19016
70.0	0.000032	62861	5.0	0.000130	15398
60.0	0.000040	50097	2.5	0.000154	12997
50.0	0.000050	40222	1.0	0.000199	10034
40.0	0.000061	32914	0.5	0.000214	9325
30.0	0.000073	27550	0.0	0.000309	6478

FEMALES (13+/NURSING)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
100.0%	0.000058	34461

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000019	106817	20.0	0.000091	21865
80.0	0.000030	66483	10.0	0.000110	18115
70.0	0.000035	57213	5.0	0.000134	14877
60.0	0.000040	50212	2.5	0.000147	13593
50.0	0.000046	43339	1.0	0.000160	12510
40.0	0.000058	34600	0.5	0.000164	12187
30.0	0.000073	27284	0.0	0.000168	11879

ACUTE EXPOSURE ANALYSIS (EX4) FOR Ethoprop — Section 3 Registration
RESIDUE FILE NAME: ETHA — Analysis Date: 8-31-93
DPR NOEL = 2.0 MG/KG BODY WT/DAY

CHILDREN (1-6 YEARS)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.9%	0.000179	11191

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000046	43609	20.0	0.000276	7252
80.0	0.000071	28000	10.0	0.000339	5894
70.0	0.000097	20600	5.0	0.000424	4713
60.0	0.000123	16253	2.5	0.000530	3771
50.0	0.000151	13284	1.0	0.000682	2932
40.0	0.000180	11122	0.5	0.000821	2436
30.0	0.000218	9162	0.0	0.002299	870

CHILDREN (7-12 YEARS)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
100.0%	0.000124	16194

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000036	55392	20.0	0.000182	10987
80.0	0.000056	36006	10.0	0.000235	8506
70.0	0.000073	27435	5.0	0.000289	6927
60.0	0.000089	22565	2.5	0.000319	6276
50.0	0.000105	18958	1.0	0.000467	4284
40.0	0.000123	16211	0.5	0.000609	3284
30.0	0.000146	13708	0.0	0.001617	1237

ACUTE EXPOSURE ANALYSIS (EX4) FOR Ethoprop — Section 3 Registration
RESIDUE FILE NAME: ETHA — Analysis Date: 8-31-93
DPR NOEL = 2.0 MG/KG BODY WT/DAY

MALES (13-19 YEARS)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MARGIN OF SAFTEY
99.9%	0.000083	24095

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000024	84457	20.0	0.000126	15932
80.0	0.000038	52763	10.0	0.000158	12629
70.0	0.000050	39962	5.0	0.000193	10387
60.0	0.000061	33040	2.5	0.000217	9219
50.0	0.000073	27576	1.0	0.000297	6727
40.0	0.000086	23155	0.5	0.000336	5944
30.0	0.000102	19623	0.0	0.000730	2738

FEMALES (13-19 YRS/NP/NN)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MARGIN OF SAFTEY
100.0%	0.000067	30005

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000015	132601	20.0	0.000104	19227
80.0	0.000025	79813	10.0	0.000132	15169
70.0	0.000035	57527	5.0	0.000159	12565
60.0	0.000045	43960	2.5	0.000197	10165
50.0	0.000056	35784	1.0	0.000245	8169
40.0	0.000066	30300	0.5	0.000360	5549
30.0	0.000081	24669	0.0	0.000686	2916

ACUTE EXPOSURE ANALYSIS (EX4) FOR Ethoprop — Section 3 Registration
RESIDUE FILE NAME: ETHA — Analysis Date: 8-31-93
DPR NOEL = 2.0 MG/KG BODY WT/DAY

MALES (20+ YEARS)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MARGIN OF SAFTEY
99.9%	0.000059	33848

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000014	148115	20.0	0.000092	21634
80.0	0.000023	86754	10.0	0.000117	17079
70.0	0.000032	62017	5.0	0.000147	13601
60.0	0.000041	49335	2.5	0.000185	10835
50.0	0.000049	40596	1.0	0.000224	8909
40.0	0.000059	33781	0.5	0.000255	7828
30.0	0.000072	27733	0.0	0.000492	4063

FEMALES (20+ YEARS/NP/NN)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MARGIN OF SAFTEY
99.6%	0.000053	37556

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000010	200624	20.0	0.000084	23723
80.0	0.000019	107312	10.0	0.000107	18681
70.0	0.000027	74369	5.0	0.000134	14914
60.0	0.000036	56134	2.5	0.000174	11499
50.0	0.000045	44828	1.0	0.000208	9612
40.0	0.000054	37010	0.5	0.000253	7911
30.0	0.000066	30372	0.0	0.000747	2678

ACUTE EXPOSURE ANALYSIS (EX4) FOR Ethoprop — Section 3 Registration
RESIDUE FILE NAME: ETHA — Analysis Date: 8-31-93
DPR NOEL = 2.0 MG/KG BODY WT/DAY

CUSTOM DEMOGRAPHICS 1: Seniors (55 + years)
All Seasons — Region(s): W — Sex: M F-all
All Races — Age-Low: 55 yrs — High: 110 yrs

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MARGIN OF SAFTEY
99.9%	0.000054	37158

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000012	168561	20.0	0.000085	23413
80.0	0.000020	100818	10.0	0.000114	17506
70.0	0.000028	71571	5.0	0.000130	15403
60.0	0.000036	55477	2.5	0.000147	13597
50.0	0.000045	44151	1.0	0.000177	11270
40.0	0.000055	36594	0.5	0.000212	9454
30.0	0.000067	29662	0.0	0.000260	7698

APPENDIX D

Annual Dietary Exposure Analyses and Residue File

ANNUAL EXPOSURE ANALYSIS (EX1) FOR Ethoprop Section 3 Registration
RESIDUE FILE NAME: ETHC Analysis Date: 8-31-93
DPR NOEL = 0.025 MG/KG BODY WT/DAY
COMMENT 1: Values equal to 50% of the tolerance
COMMENT 2: All label-approved uses for ethoprop

RESIDUE FILE LISTING

TAS CODE	EPA CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ #1	FCTRS #2	SOURCE CODE
71	06002AA	A	BANANAS-OTHER VARIETIES	0.010000	1.00	1.00	EPA
72	06002AB	A	BANANAS	0.010000	1.00	1.00	EPA
73	06002DA	A	BANANAS-DRIED	0.010000	3.90	1.00	EPA
89	06013AA	A	PINEAPPLES-PEELED FRUIT	0.010000	1.00	1.00	EPA
90	06013DA	A	PINEAPPLES-DRIED	0.010000	0.00	1.00	EPA
91	06013JA	A	PINEAPPLES-JUICE	0.010000	1.70	1.00	EPA
148	10010AA	J	CUCUMBERS	0.010000	1.00	1.00	EPA
170	13007AA	F	CABBAGE-GREEN AND RED	0.010000	1.00	1.00	EPA
173	13010AA	F	CABBAGE-CHINESE/CELERY/BOK CH	0.010000	1.00	1.00	EPA
207	14013AA	B	POTATOES(WHITE)-WHOLE	0.010000	1.00	1.00	EPA
208	14013AB	B	POTATOES(WHITE)-UNSPECIFIED	0.010000	1.00	1.00	EPA
209	14013AC	B	POTATOES(WHITE)-PEELED	0.010000	1.00	1.00	EPA
210	14013DA	B	POTATOES(WHITE)-DRY	0.010000	6.50	1.00	EPA
211	14013HA	B	POTATOES(WHITE)-PEEL ONLY	0.010000	1.00	1.00	EPA
218	14018AA	B	SWEET POTATOES (INCLUDING YAM	0.010000	1.00	1.00	EPA
229	15001AC	G	BEANS-DRY-LIMA	0.010000	1.00	1.00	EPA
233	15002AA	G	BEANS-SUCCULENT-LIMA	0.010000	1.00	1.00	EPA
235	15003AB	G	BEANS-SUCCULENT-OTHER	0.010000	1.00	1.00	EPA
237	15004AA	O	CORN/POP	0.010000	1.00	1.00	EPA
238	15005AA	O	CORN/SWEET	0.010000	1.00	1.00	EPA
239	15006AA	A	PEANUTS-WHOLE	0.010000	1.00	1.00	EPA
245	15015AA	A	OKRA	0.010000	1.00	1.00	EPA
255	15029AA	G	SOYBEANS-SPROUTED SEEDS	0.010000	0.33	1.00	EPA
261	16003AA	A	MUSHROOMS	0.010000	1.00	1.00	EPA
266	24002EA	O	CORN/GRAIN-ENDOSPERM	0.010000	1.00	1.00	EPA
267	24002HA	O	CORN/GRAIN-BRAN	0.010000	1.00	1.00	EPA
268	24002SA	O	CORN SUGAR	0.010000	1.50	1.00	EPA
283	25003SA	A	CANE SUGAR	0.010000	1.00	1.00	EPA
289	27002OA	O	CORN GRAIN-OIL	0.010000	1.00	1.00	EPA
293	27007OA	A	PEANUTS-OIL	0.010000	1.00	1.00	EPA
297	27010OA	G	SOYBEANS-OIL	0.010000	1.00	1.00	EPA
303	15023AA	G	SOYBEANS-UNSPECIFIED	0.010000	1.00	1.00	EPA
304	28023AB	G	SOYBEANS-MATURE SEEDS DRY	0.010000	1.00	1.00	EPA
305	28023WA	G	SOYBEANS-FLOUR (FULL FAT)	0.010000	1.00	1.00	EPA
306	28023WB	G	SOYBEANS-FLOUR (LOW FAT)	0.010000	1.00	1.00	EPA
307	28023WC	G	SOYBEANS-FLOUR (DEFATTED)	0.010000	1.00	1.00	EPA
378	06002NA	A	BANANAS-NECTAR	0.010000	1.00	1.00	EPA
383	13007SA	F	CABBAGE-SAVOY	0.010000	1.00	1.00	EPA
388	24002MO	O	CORN SUGAR-MOLASSES	0.010000	1.50	1.00	EPA
403	15006BT	A	PEANUT-BUTTER	0.010000	1.89	1.00	EPA
406	06013JC	A	PINEAPPLES-JUICE-CONCENTRATE	0.010000	6.30	1.00	EPA
911	NOCODE	A	MOLASSES-NFS	0.010000	1.00	1.00	EPA
940	NOCODE	A	PEANUTS HULLED	0.010000	1.00	1.00	EPA

ANNUAL EXPOSURE ANALYSIS (EX1) FOR Ethoprop Section 3 Registration
RESIDUE FILE NAME: ETHC Analysis Date: 8-31-93
DPR NOEL = 0.025 MG/KG BODY WT/DAY
COMMENT 1: Values equal to 50% of the tolerance
COMMENT 2: All label-approved uses for ethoprop

TOTAL EXPOSURE BY POPULATION SUBGROUP

POPULATION SUBGROUP	TOTAL EXPOSURE MG/KG BODY WT/DAY	MARGIN OF SAFETY[1]
U.S. POP - 48 STATES - ALL SEASONS	0.000037	676
U.S. POPULATION - SPRING SEASON	0.000037	676
U.S. POPULATION - SUMMER SEASON	0.000040	625
U.S. POPULATION - AUTUMN SEASON	0.000036	694
U.S. POPULATION - WINTER SEASON	0.000036	694
NORTHEAST REGION	0.000036	694
NORTH CENTRAL REGION	0.000037	676
SOUTHERN REGION	0.000040	625
WESTERN REGION	0.000034	735
HISPANICS	0.000034	735
NON-HISPANIC WHITES	0.000037	676
NON-HISPANIC BLACKS	0.000040	625
NON-HISPANIC OTHER THAN BLACK OR WHITE	0.000039	641
NURSING INFANTS (<1 YEAR OLD)	0.000025	1000
NON-NURSING INFANTS (<1 YEAR OLD)	0.000084	298
FEMALES (13+/PREGNANT/NOT NURSING)	0.000027	926
FEMALES (13+/NURSING)	0.000027	926
CHILDREN (1-6 YEARS)	0.000086	291
CHILDREN (7-12 YEARS)	0.000060	417
MALES (13-19 YEARS)	0.000041	610
FEMALES (13-19 YRS/NOT PREG. OR NURSING)	0.000031	806
MALES (20+ YEARS)	0.000029	862
FEMALES (20+ YEARS/NOT PREG. OR NURSING)	0.000026	962

DATE: 01/09/1995 TIME: 09:42:52

GLOBAL 86 (MAY 1986)

Ethoprop; M rats oral; m-pheochromocytoma

POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=0)
MONTE CARLO TEST USED IN SELECTION

GROUP	DOSE	#RESPONSES OBSERVED/#ANIMALS	#RESPONSES PREDICTED
1	.000000	0/ 48	1.13
2	3.000000E-02	2/ 48	1.14
3	2.10000	2/ 49	1.57
4	16.2000	5/ 60	5.16

CHI-SQUARE GOODNESS OF FIT STATISTIC IS 1.9565

P-VALUE FOR THE MONTE CARLO TEST IS .4500000000

FORM OF PROBABILITY FUNCTION:
P(DOSE) = 1 - exp(-Q0 - Q1 * D - Q2 * D^2)

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = 2.391215329564E-02
Q(1) = 4.071984023119E-03
Q(2) = .000000000000

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -35.3601470318

CALCULATIONS ARE BASED UPON EXTRA RISK
LINEARIZED MULTISTAGE CONFIDENCE LIMITS

****

RISK	MLE DOSE	LOWER BOUND ON DOSE	UPPER BOUND ON RISK	CONFIDENCE LIMIT SIZE
.10000	25.874	13.095	.18794	90.0
		11.240	.21537	95.0
		9.9370	.23993	97.5
		8.6907	.26925	99.0
1.00000E-02	2.4682	1.2492	1.96623E-02	90.0
		1.0721	2.28712E-02	95.0
		.94789	2.58302E-02	97.5
		.82901	2.94791E-02	99.0
1.00000E-03	.24570	.12435	1.97491E-03	90.0
		.10673	2.30059E-03	95.0
		9.43612E-02	2.60177E-03	97.5
		8.25271E-02	2.97430E-03	99.0
1.00000E-04	2.45593E-02	1.24296E-02	1.97577E-04	90.0
		1.06683E-02	2.30194E-04	95.0
		9.43187E-03	2.60365E-04	97.5
		8.24899E-03	2.97695E-04	99.0
1.00000E-05	2.45582E-03	1.24290E-03	1.97586E-05	90.0
		1.06678E-03	2.30207E-05	95.0
		9.43145E-04	2.60384E-05	97.5
		8.24862E-04	2.97722E-05	99.0
1.00000E-06	2.45581E-04	1.24290E-04	1.97587E-06	90.0
		1.06677E-04	2.30209E-06	95.0
		9.43141E-05	2.60386E-06	97.5
		8.24859E-05	2.97724E-06	99.0
1.00000E-07	2.45581E-05	1.24290E-05	1.97587E-07	90.0
		1.06677E-05	2.30209E-07	95.0
		9.43140E-06	2.60386E-07	97.5
		8.24858E-06	2.97725E-07	99.0
1.00000E-08	2.45581E-06	1.24290E-06	1.97587E-08	90.0
		1.06677E-06	2.30209E-08	95.0
		9.43140E-07	2.60386E-08	97.5
		8.24858E-07	2.97725E-08	99.0

END OF LINEARIZED MULTISTAGE CONFIDENCE LIMITS

****

GLOBAL 86 LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK
****

RISK	MLE DOSE	LOWER BOUND ON DOSE	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
1.00000E-05	2.45582E-03	1.06678E-03	95.0%	Q(0) = 1.69332E-02 Q(1) = 9.37407E-03 Q(2) = .00000
1.00000E-06	2.45581E-04	1.06677E-04	95.0%	Q(0) = 1.69332E-02 Q(1) = 9.37407E-03 Q(2) = .00000

GLOBAL 86 UPPER CONFIDENCE LIMITS ON RISK FOR FIXED DOSE
****

DOSE	MLE RISK	UPPER BOUND ON RISK	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
3.0000	1.21416E-02	2.77305E-02	95.0%	Q(0) = 1.69332E-02 Q(1) = 9.37407E-03 Q(2) = .00000
5.00000E-08	2.03599E-10	4.68704E-10	95.0%	Q(0) = 1.69332E-02 Q(1) = 9.37407E-03 Q(2) = .00000

NORMAL COMPLETION!